ARCHIVES OF PATHOLOGY

VOLUME 17 APRIL, 1934 NUMBER 4

EXPERIMENTAL ATHEROSCLEROSIS IN THE RABBIT COMPARED WITH HUMAN (CORONARY) ATHEROSCLEROSIS

TIMOTHY LEARY, M.D.

BOSTON

The literature on arteriosclerosis has been so recently and thoroughly reviewed in the book on this subject issued by the Josiah Macy, Jr., Foundation [1] that a detailed discussion is unnecessary. The *lipoid* relations of the common form of the disease have been investigated by chemical tests which revealed the high content of lipoids in atheromatous aortae. The Aschoff-Virchow theory separated atherosclerosis from the other forms of arteriosclerosis. The experimental production of atherosclerosis in rabbits by feeding them cholesterol, reviewed by Anitschkow,[1] was largely the work of the Russian school. Wolkoff [2] studied the evolution of changes in human coronary arteries with age, the distribution of lipoids in these arteries and their branches, and the production of experimental coronary atherosclerosis in the rabbit.

Practically all of the chemical work, most of the experimental research and much of the morphologic studies have dealt with the lesions of the aorta. From the standpoint of its effect on human life atherosclerosis of the aorta is of relatively minor importance. Moreover, the aorta is of highly complex structure histologically and is extremely rich in elastica. Atherosclerosis of the coronary arteries is of primary importance from the point of view of human disease. The coronary arteries are of relatively simple structure histologically; they are muscular arteries, poor in elastica. The simplicity of structure of these vessels permits of more exact appraisement of the origin, progress and character of the lesions of atherosclerosis than is possible in the aorta.

The coronary arteries differ from other muscular arteries in developing a layer of unstriped muscle and cellular subendothelial fibrous tissue. This is without a circulation of its own, depending for nutrition on imbibition

From the Medical Examiner Service, Suffolk County, Southern District,

Aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Anitschkow, in Cowdry, Edmund V.: Arteriosclerosis: A Review of the Problem, New York, The Macmillan Company, 1933.

2. Wolkoff, C.: (*a*) Virchows Arch. f. path. Anat. **241**:42, 1923; (*b*) Beitr. z. path. Anat. u. z. allg. Path. **82**:555, 1929; (*c*) ibid. **85**:386, 1930.

through the endothelium. That the buffer layer in the coronary arteries is a response to the unusual stresses which these vessels are called on to bear seems reasonable. It is now generally agreed that the main coronary vessels and their branches, which lie in the subepicardial fat, are filled with blood during systole. Per contra, the finer branches in the myocardium are compressed and may be closed by the contracting muscle during systole. At the end of systole the aortic cusps are closed and the highest point of aortic pressure is momentarily produced. It is this peak pressure which is believed to cause the rupture of aortic aneurysms. With the diastolic relaxation of the heart muscle the intramural branches of the coronary arteries are freed from compression and are filled with blood, the maximal flow occurring during this period. Throughout a part of the cardiac cycle the main coronary arteries and their epicardial branches are meeting high pressure from the blood-filled aorta and resistance from their compressed intramural branches.

It is recognized that the proximal inch of the left coronary artery and its descending branch is the favorite region of localization of coronary atherosclerosis in its most extreme form. This is the standard site of coronary thrombosis. A probable factor of importance in this regard is the character of the curve which this part of the vessel takes in its descending course. Coming off at right angles to the aortic wall, this portion of the vessel describes a curve which brings it rather abruptly to a course parallel to that of the aortic wall. It is believed that the localization of atherosclerosis and of syphilitic aortitis with resulting aneurysms in the aortic arch is related to the curve which the aorta takes and to the high and varied pressures produced in this part of the vessel. The curve of the left coronary artery in its proximal portion is quite sharp and, perhaps, comparable to that of the ascending portion of the aortic arch. Moreover, a large branch of the left coronary artery, the circumflex, arises near the orifice at right angles to the main vessel. The right coronary artery changes direction only slightly from its origin, is usually a relatively straight vessel for a large part of its course, and gives off no large branches in its proximal portion.

In the following paper three series of observations are recorded:

I. Human coronary sclerosis.

II. Experimental atherosclerosis in the rabbit

III. A comparison of human and experimental rabbit atherosclerosis in the coronary arteries

I. HUMAN CORONARY SCLEROSIS

The study of a large series of coronary arteries, lesions of which had led to a fatal termination, demonstrated that the histologic changes

which the vessels had undergone caused them to fall into two groups. This histologic division corresponded closely to a difference in the ages of the subjects represented in the two groups. The first group, in which the dominant change in the coronary arteries consisted of fibrosis leading to narrowing of the lumen, represented persons from 25 to 55 years of age. The second group in which the dominant change consisted of collections of lipoid cells with a tendency to atheromatous necrosis, giving rise to so-called atheromatous "abscesses," represented persons from the age of 47 years up to extreme old age.

There were two exceptions to this rule in the series, occurring in young men, but a reason for these exceptions is made clear in the case records (cases 20 and 21).

It is indicated that the lesions in the first group represent a reaction of youth. The lesions in the second group depend apparently on a lack of this reaction at older ages.

The following cases were selected only because of the necessary limitations of illustration, save that in the first group the cases of the youngest patients have been reported.

GROUP 1 (FIG. 1)

CASE 1.—A man, aged 25, an athlete, who had had no previous illness save one attack of indigestion two weeks before death, was playing baseball as usual on Sunday, the day of his death. He made a hit, ran to second base and collapsed. The heart weighed 405 Gm. The conditions found were: *high grade sclerosis of the left coronary artery, descending branch* (fig. 1 *A*), *with thrombosis at a higher level;* fibrosis with occlusion of the circumflex branch; moderate sclerosis of the right coronary artery, and myocardial atrophy with repair (chronic myocarditis) near the apex. The aorta was thin, smooth and elastic save for one raised scar, 2.5 cm. in diameter, 3 cm. above the bifurcation; the aorta showed a rather diffuse yellow opacity, notably about the orifices of vessels, and several small gray regions with little projection.

CASE 2.—A man, 26 years of age, a chauffeur, had had an occasional attack of acute indigestion. He was removing a wheel from an automobile when he collapsed and within a few minutes, when a doctor could be found, was pronounced dead. The heart weighed 415 Gm. and presented a *high grade sclerosis with thrombosis of the descending branch of the left coronary artery* (fig. 1 *B*). There was also marked sclerosis of the circumflex branch and the right coronary artery. The aorta was thin, smooth and elastic, with delicate yellow streaks along the lines of the intercostal orifices—not raised.

CASE 3.—A man, 28 years old, a clerk, felt a sudden onset of precordial pain and anxiety. He sat bent forward with hands on chest at home for four hours. He was admitted to a hospital, where he sat in bed in a similar position for one hour and twenty minutes before death. The heart weighed 340 Gm. and showed *fibrous sclerosis and thrombosis of the descending branch of the left coronary artery for 1 cm., beginning 1.5 cm. from the orifice* (fig. 1 *C*). There was gross occlusion of the circumflex branch 3 cm. from the orifice. Opaque yellow patches were scattered throughout all the coronary vessels, but the lumens elsewhere were free. The aorta was thin, smooth and elastic.

CASE 4.—A man, aged 31, a stationary engineer, did not feel well, and drank tea and chicken soup. He lay down and "had a fit," dying suddenly about one hour and fifty minutes after he began to feel badly. There had been no previous

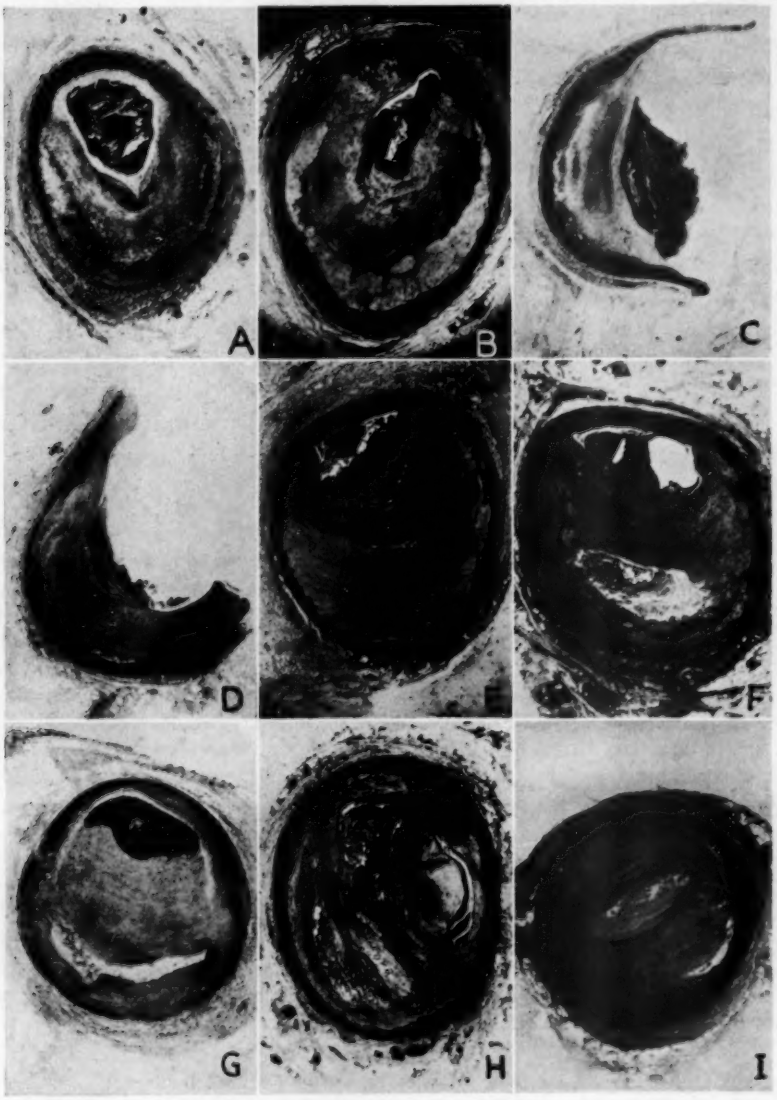

Fig. 1.—Group 1. Fibrosis, the reaction of youth. Thromboses in cases 1 to 8 are shown in *A* to *H* inclusive. Coronary insufficiency in case 9 is shown in *I*.

symptoms. *The descending branch of the left coronary artery showed eccentric thickening with thrombosis over a region 0.7 cm. long, beginning 1.3 cm from the orifice* (fig. 1 *D*). The aorta was smooth and elastic, with two thick circular fibrous plaques in the arch.

CASE 5.—A woman, 34 years of age, married, had nephritis of pregnancy one year before death. Several years prior to death she had had an operation for gallstones. Four days before death she had pain in the left side of the chest extending to both arms and upward to the neck. No dyspnea accompanied this. She went to a physician's office. The pain was relieved by morphine. The pulse was of good quality and regular during the attack. She suffered a second attack of pain two days before death, also relieved by morphine. The pain recurred early in the morning. While talking with her husband she suddenly collapsed and died. The heart weighed 400 Gm. and showed acute fibrinous pericarditis. There was an infarction of the wall of the left ventricle from the apex upward, including the left portion of the septum, to within 2 cm. of the aortic cusps. *The descending branch of the left coronary artery showed eccentric thickening, beginning 1.5 cm. from the orifice. The lumen was closed by a thrombus 2 cm. from the orifice* (fig. 1 *E*). There was generalized patchy thickening of the walls of both coronary arteries, most marked in the left coronary artery. The aorta was thin, smooth and elastic save for a scar 5 cm. by 1 cm. in the abdominal portion of the vessel and a few small plaques of lime salts above the bifurcation. There were regions of yellow opacity without projection about the orifices of the branches.

CASE 6.—A man, 37 years of age, a laborer, who had had no symptoms, but who had been drinking alcoholic liquor, went to bed at 11 p. m. At 2:45 a. m. he snored so violently that his wife became alarmed and called a doctor who on arrival pronounced the man dead. The heart weighed 430 Gm. *In the left coronary artery together with the descending and circumflex branches there was eccentric thickening, with thrombosis of the descending branch near the origin* (fig. 1 *F*). The right coronary artery showed some thickening of the wall, but the lumen was large and clear. The aorta showed patches of yellow opacity, without thickening about the ring, and pinhead-sized yellow opaque regions scattered in the arch, about the orifices of the intercostal branches and almost continuous in the abdominal portion of the vessel. Apart from these deposits, which did not project, the aorta was thin, smooth and elastic.

CASE 7.—A man, aged 38, an attendant in an automobile parking space, with no previous illnesses, went into a restaurant, complaining of indigestion, and asked for sodium bicarbonate in water, which he drank. He walked a short distance to an express office, sat down in a chair and then collapsed on the floor —all within ten minutes. The heart weighed 390 Gm. The coronary orifices were small, in scarred areas in the aortic ring. *The descending branch of the left coronary artery was narrowed almost to occlusion with thrombosis for 0.8 cm., beginning 1.5 cm. from the coronary orifice* (fig. 1 *G*). Patches of irregular thickening were scattered through the coronary vessels. A series of raised gray scars and yellow opaque foci were present in the thoracic and upper abdominal regions of the aorta. A ruptured atheromatous focus, 2.5 cm. by 2 cm., covered with translucent gray-red clot overlying red clot, was found in the midabdominal part of the vessel.

CASE 8.—A man, 38 years old, an automobile mechanic, lived at the top of a hill 100 ft. (30 meters) high, with a steeply graded approach. He came up the hill rapidly and said that his heart bothered him. He later got out of bed and sat at a window two hours. The next day he saw a physician, who found a tachycardia, which was relieved by morphine. Two days later he was seized with pain in the chest and took a Seidlitz powder. He suddenly fell to the floor and when a doctor arrived, within a few minutes, he was pronounced dead. The heart weighed 320 Gm. *The descending branch of the left coronary artery was found*

almost completely occluded for 2 cm., beginning 2 cm. from the coronary orifice, with a sharply localized clot 2.5 cm. from the orifice (fig. 1 *H*). The proximal portion of the circumflex branch was similarly narrowed. The condition of the right coronary artery was not recorded. The aorta showed opaque yellow patches in the descending arch, with streaks along the intercostal orifices. There were several gray scars in the abdominal portion of the vessel.

CASE 9.—This was an instance of coronary insufficiency. A man, aged 41, a mechanic, had had neuritis for one year. Apart from this he had not had any reason to consult a doctor for many years. There had been no indigestion. He started to walk to work with a fellow workman on a cold morning. He collapsed on the street and died suddenly. The heart weighed 370 Gm. There was eccentric yellow thickening in regions of the wall of the left coronary artery, but the lumen was of moderate size and clear. *In the right coronary artery there was almost complete obliteration of the lumen for 2 cm., beginning 2 cm. from the orifice. There was no thrombosis* (fig. 1 *I*). Beyond this point the walls were slightly thickened and showed some calcification. The arch of the aorta was beset with many pinhead-sized yellow foci. In the thoracic region occurred yellow streaks and pale gray larger patches over deep yellow deposits. The surface over the pale gray regions was edematous, and section disclosed mucoid swelling of the tissues. In the abdominal portion of the vessel similar patches of gray scarring and several larger soft atheromatous foci were present.

SUMMARY OF OBSERVATIONS IN GROUP 1

Nutrition of the New Tissue.—The nutrition of the new fibrous tissue in this group depended in its early stages on imbibition from the blood circulating in the lumen. Ultimately, as the fibrous layer increased, this became inadequate and necrosis resulted. In each of the vessels shown in figure 1 there was a zone of necrosis, which tended to be crescentic and which affected the layer farthest from the lumen, i. e., next to the media. In coronary artery *E* (fig. 1) there was massive necrosis including most of the new tissue. In the coronary arteries exhibiting the standard crescentic necrosis small groups of cells directly next to the media sometimes survived, particularly if vasa vasorum were present.

More interesting, however, was the formation in the more central layers, near the lumen, of a capillary circulation. This capillary layer seemed to be cut off by the zone of necrosis from any connection with the outer wall and a circulation through possible vasa vasorum. Search of series of sections revealed a direct connection of this capillary layer with the coronary lumen. This is best illustrated in the coronary artery of a painter, 55 years of age, who died suddenly without previous symptoms (case 10). Here the central capillary zone was large (fig. 2). Such a capillary circulation was found in coronary arteries *B*, *C*, *D* and *G* (fig. 1). In coronary artery *A* no vessels were found in the new intimal tissue. In coronary artery *G* vasa vasorum supplied the outer layer as well. In coronary arteries *F*, *H* and *I* what circulation was present came from vasa vasorum. In coronary artery *E* no vasa

vasorum were found, but groups of cells survived along the medial junction in a relation suggesting their possible influence.

Elastica.—As was to be expected, the internal elastic lamina in the advanced processes in these terminal conditions showed fragmentation and flattening. It even disappeared in regions where the fibrous layer

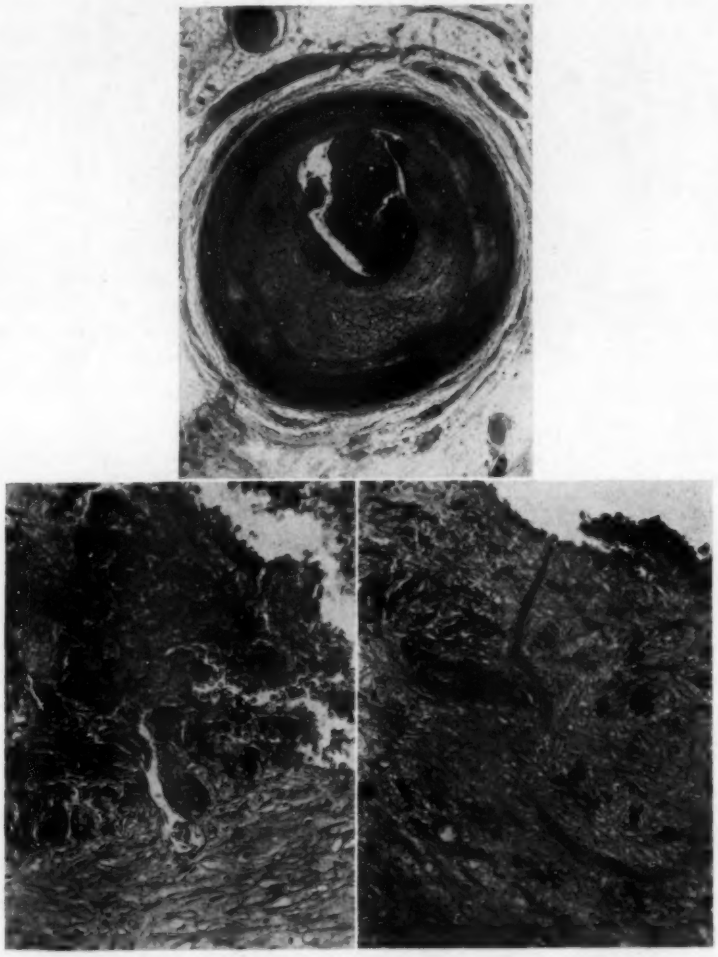

Fig. 2.—Central capillary circulation connecting with lumen of coronary artery in case 10, with two capillaries opening on surface.

had crossed its site and invaded the media. Only occasionally was there evidence of reduplication.

Sections from smaller branches of the coronary arteries, in which the process was seen in earlier stages, disclosed in the earliest processes an almost intact elastic lamina (fig. 3 *A*). Even in advanced processes

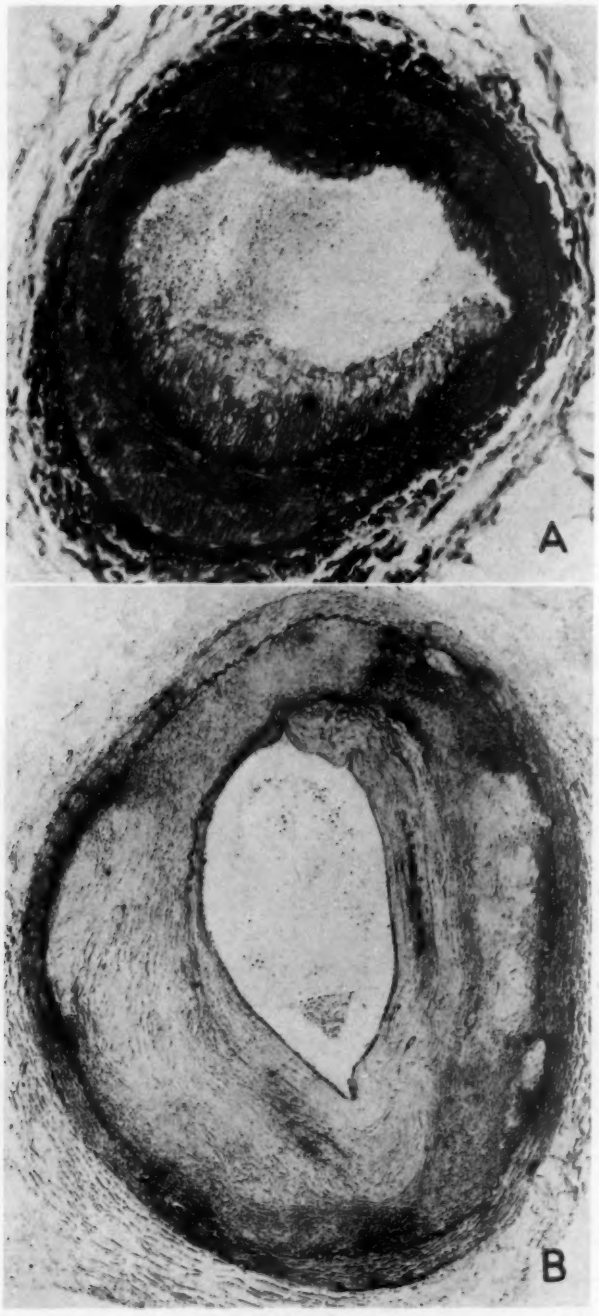

Fig. 3.—*A*, branch of human coronary artery; × 90; early fibrosis with lipoid cells; elastica almost intact. *B*, left descending branch of human coronary artery; × 50; advanced fibrosis, elastica in normal locus, somewhat fragmented and broken; media intact.

the elastic lamina was sometimes found in its normal locus and, though somewhat flattened and fragmented, gave evidence of its resiliency by its wavy outline (fig. 3 *B*). The principal changes in the elastica occurred where fibrous tissue from the intima invaded its site. While conditions of stress favor the localization of lesions in the arteries, definite morphologic evidence of injury to the elastica is not constant.

Media.—The media in the left coronary artery in case 2 (fig. 1 *B*) showed general hypertrophy. Hypertrophy in part was shown in others, as in that in case 1 (fig. 1 *A*). There was invasion of the media by connective tissue in the lower segment of this artery, and varying degrees of local invasion, thinning or hypertrophy in all of the others of the group. As was true of the elastica, examination of sections of early lesions disclosed no evidence of medial injury or reaction. The lesions of the media appear to be secondary to the intimal process.

Cellular Inflammatory Reaction.—Varying degrees of lymphoid cell infiltration of the intima were seen in this group. In the left coronary artery in case 1 (fig. 1 *A*) a rare lymphoid cell occurred in the more central portion of the thickened intima, and a rare small group near the media. In the other arteries in this group a more considerable degree of infiltration appeared, particularly near the regions of necrosis, and in some cases near the thrombosed lumen.

There was no lymphoid cell infiltration of the media in the left coronary arteries in cases 1, 2, 3, 4, 5 and 8 (fig. 1 *A, B, C, D, E* and *H*). There were focal collections of cells in the artery in case 6 (fig. 1 *F*) and diffuse infiltration in that in case 7 (fig. 1 *G*).

Perivascular collections of lymphoid cells occurred in the adventitia of all of the coronary arteries in the group save those from cases 1 and 4 (fig. 1 *A* and *D*).

Studies of early processes in branches of the coronary arteries, where the lesions were still proliferative and without necrosis, revealed no lymphoid cell invasion or other evidences of inflammatory reaction.

The relation of the lymphoid cell infiltration to the advanced lesions, in which necrosis had occurred, makes it probable that the inflammatory reactions arise in this disease as a response to the presence of necrotic tissue products. The inflammatory reaction is therefore secondary and usually late. This is consistent with the finding of MacCallum [1] that infections probably do not play a great part in the pathogenesis of arteriosclerosis.

Calcification.—Tangible deposits of lime salts did not occur in the coronary arteries of the first group. A minor degree of calcification was found in the arteries from some of the older cases of group 2. Calcification is in general a much later phenomenon in the coronary arteries than in the aorta. From the standpoint of etiology it is of little

significance. Jenner's famous letter has influenced clinicians to look on calcification as of particular importance in coronary disease. The tissue deposit of lime salts is always of monumental character, marking the site formerly occupied by living tissue. In some cases of coronary disease it may serve, as an end-result, to prevent coronary spasm, and thus, perhaps, delay the fatal termination.

Lipoid Cell Infiltration.—Lipoid cell groups, usually small, were found in all the coronary arteries in this group, and definite atheromatous regions of liquefaction were present in the coronary arteries from cases 6 to 9 (fig. 1 *F, G, H* and *I*). The process was dominantly fibrous, however, even in these vessels, particularly about the lumens.

Fig. 4.—Subendothelial V-shaped region of necrosis from case 1; stained with Weigert's stain for fibrin.

The intimate relation of lipoid cells to the new growth of fibrous tissue was manifest in all of these vessels. It was best illustrated, however, in early lesions in the smaller branches of the coronary arteries. Discussion of this relation is deferred to the second section of this paper where comparative illustrations make the process more clear.

Cause of Thrombosis.—In the left coronary arteries in cases 1, 2, 4, 5, 6 and 8 (fig. 1 *A, B, D, E, F* and *H*) there occurred regions of fibrinous or fibrinoid [3] necrosis arising in the subendothelial tissues and extending to the intima (fig. 4). The material saved in cases 3 and 7

3. The material reacts in some cases completely and in others incompletely to Weigert's stain for fibrin.

was minimal; it is possible that further sections would have disclosed this lesion. Its occurrence in six of the eight arteries illustrated, a percentage which corresponds to that found at older ages, suggests that this is the lesion which leads to thrombosis when the necrosis reaches the endothelial layer. This reasoning is based on the belief that endothelial necrosis leads to thrombosis. The subendothelial and the endothelial processes may have been produced simultaneously. It is difficult to account for the subendothelial lesion as a sequence of an endothelial necrosis.

GROUP 2 (FIG. 5)

CASE 11.—A retired business man, 61 years of age, with no record of illness, collapsed on the street. He was brought to the hospital by the police and there was pronounced dead. The heart weighed 425 Gm. The coronary arteries showed regions of narrowing almost to occlusion, notably of the descending branch of the left coronary artery and particularly just below the origin of the circumflex branch. The circumflex branch showed thickening with calcification, as did the right coronary artery. The size of the lumen in some regions was, however, almost normal. The heart showed atrophy with fibrosis over the left wall of the left ventricle extending onto the septum, with atrophy of the left papillary muscle. There was high grade sclerosis, with scarring and plaques of lime salts, throughout the aorta. Figure 5*A* shows *an unruptered atheromatous "abscess" in the proximal portion of the descending branch distorting the lumen, which lay to the left and above. The vessel was obliterated by fibrosis below.*

CASE 12.—A man, aged 50, an engineer in an ice plant, with no previous complaints, had a pain in the chest and was taken by his son in an automobile to a doctor's office. He collapsed in the automobile and was pronounced dead. The heart weighed 380 Gm. There was narrowing of the descending branch of the left coronary artery almost to occlusion 1.5 cm. below the orifice. Below this the lumen was the size of a small pin; it then widened to a moderate size. In the circumflex branch and the right coronary artery occurred patches of yellow thickening, but the lumen of the right coronary artery was large. The aorta in general was smooth, with a large scar at the junction of the ductus arteriosus. Yellow opaque regions without projection were present in the arch and in the thoracic regions of the vessel, and slightly raised opaque yellow regions in the abdominal portion of the vessel, with three scars, two of them large, extending into the iliac vessels. Figure 5*B* shows *a large, almost empty, atheromatous "abscess" to the right and below. The lumen to the left and above contains a thrombus including lipoid cells.*

CASE 13.—A man, 60 years of age, an appliance mechanic employed by a gas company, had had pain in the chest for two weeks. He went to work at 9 a. m., returned home at 11 a. m., and had a typical attack of angina. He was found dead at 5.15 p. m. The heart weighed 656 Gm. In the descending branch of the left coronary artery was a clot 2 cm. from the orifice in a region of narrowing. In the lower two thirds of its course the vessel showed almost complete obliteration. The circumflex branch and the right coronary artery showed minor sclerosis. The myocardium was thinned, with fibrosis over the left wall of the left ventricle and the neighboring septum. In the aorta there was a relatively minor degree of sclerosis, with rather abundant yellow opaque patches. Figure 5*C* shows *the point of rupture of an atheromatous "abscess," to the right and below,*

into the lumen, to the left and above. Thrombosis and atheromatous contents were found below this level.

CASE 14.—A man, aged 51, an inspector of water meters, collapsed in a house after coming upstairs from the cellar, where he had inspected the meter. There

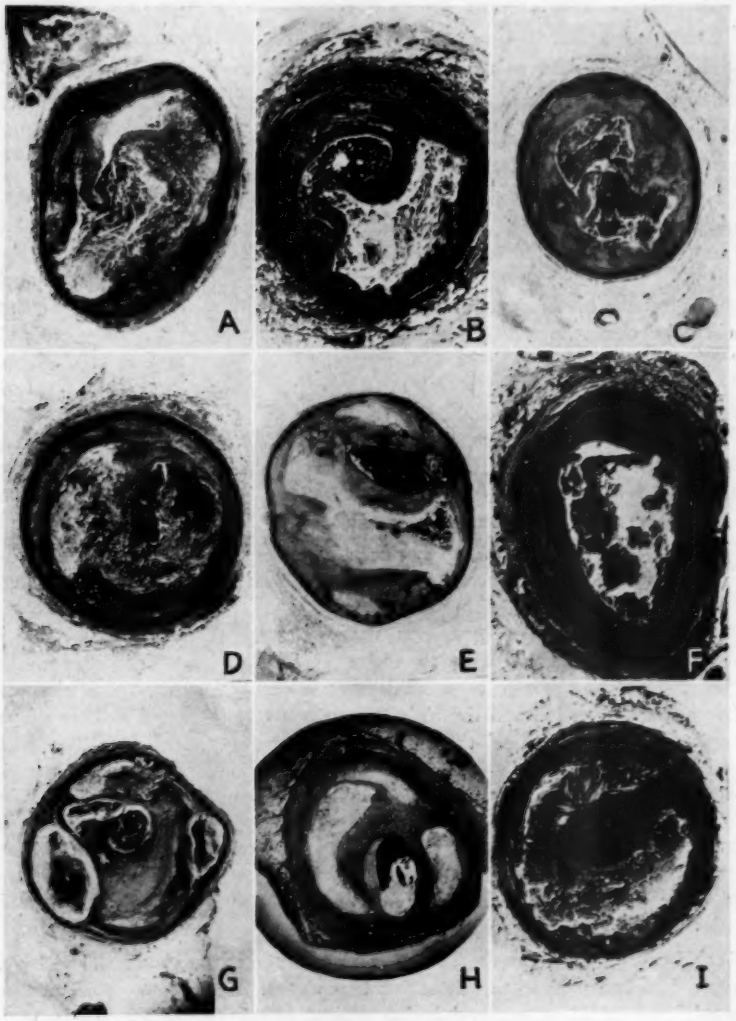

Fig. 5.—Group 2. Atheromatosis—lack of reaction in age. Rupture of or into atheromatous pockets, with thrombosis, in all cases save case 11 (*A*) and case 19 (*I*). In the latter cases death was due to coronary insufficiency.

was no history of illness. He was pronounced dead on arrival at the hospital. The heart weighed 400 Gm. There was scarring of the aortic ring with narrowing about the coronary orifices, notably the right. There was narrowing of the lumen of the descending branch of the left coronary artery, with almost

complete occlusion 2 cm. from the orifice. In the circumflex branch there was eccentric thickening of the wall. The right coronary artery, a vessel of normal caliber beyond the narrowed orifice, exhibited minor thickenings of the wall with a clear lumen. Moderate sclerosis of the aorta was present about the orifices of branches. Figure 5 *D* shows *a large atheromatous "abscess" to the right and below rupturing through necrotic regions, shown by deep staining fibrin, into the narrow lumen above to the right. A platelet clot is seen in the lumen.*

CASE 15.—A man, 58 years old, a shoe manufacturer, was attending a convention. He had had slight indigestion at times. He collapsed in a hotel and was pronounced dead by a physician almost immediately. The heart weighed 320 Gm. There was narrowing of the lumen of the descending branch of the left coronary artery with calcification and thrombosis of the narrowed lumen 3 cm. from the orifice. In the circumflex branch there was apparent occlusion 0.5 cm. from its origin. The condition of the aorta was not recorded. Figure 5 *E* shows *a rupture of lumen into a pocket filled with lipoid cells, above to the right; fibrin bands spreading fanlike from the point of rupture and occluding the lumen, and a large atheromatous "abscess," below.*

CASE 16.—A man, aged 50, a dress designer, collapsed at work, and when the doctor arrived, within five minutes, was pronounced dead. There was no history of illness. The heart weighed 330 Gm. In the descending branch of the left coronary artery, beginning 1 cm. from the orifice, was a clot extending 1 cm. Patches of concentric and eccentric thickening occurred in all of the coronary vessels, with small but patent lumens. Regions of yellow opaque thickening occurred in the arch and the thoracic portions of the aorta. In the abdominal portion of the vessel opaque yellow regions and gray scars with some calcified plaques were almost continuous. Figure 5 *F* shows *a rupture of a massive atheromatous "abscess" occupying most of the vessel through a tear (left) in its thin wall into the compressed lumen, which is to the left and above.*

CASE 17.—A man, aged 62, was a concessionaire in a baseball park. He had an attack of angina one year before death. He was overweight. He had lost 18 pounds (8.2 Kg.) recently on advice of a doctor. He worked hard the day before death, and ate a heavy evening meal. He was found dead in the morning. The heart weighed 500 Gm. There was marked concentric thickening of the descending branch of the left coronary artery. The circumflex branch was narrowed apparently to obliteration about 3 cm. from its origin and contained clot beyond that region. In the right coronary there was eccentric thickening of the wall with an apparently double lumen at one point containing clot. There was some thinning with myocardial atrophy and scarring over the right wall of the left ventricle extending onto the septum, as well as atrophy of the right papillary muscle. In the thoracic portion of the aorta occurred large, raised atheromatous patches, the largest 3.5 cm. in diameter. In the abdominal portion of the vessel were yellow opaque streaks above and larger raised yellow patches below, the area above the bifurcation being relatively free. Figure 5 *G* shows *four atheromatous foci. The lumen in the center is seen filled with a thrombus and material from an atheromatous cavity.*

CASE 18.—A man, aged 66, a painter, was arrested for drunkenness. He had made no complaints of illness. He talked with a fellow prisoner thirty minutes before he was found lying on the cot in his cell, dead. The heart weighed 290 Gm. There was narrowing of the descending branch of the left coronary artery, with almost complete obstruction 2 cm. from the orifice. The wall was gray and opaque. The vessel below was filled with clot. In the right coronary artery

no gross evidence of sclerosis was found. Figure 5 *H* shows *atheromatous "abscesses" on both sides of the central lumen, which contains atheromatous material below and a thrombus above.*

CASE 19.—This was an instance of coronary insufficiency. A man, 60 years of age, a waiter, collapsed while working in a lunchroom and died immediately. He had been in apparently good health, save for complaints about his teeth. The heart weighed 380 Gm. Small gray fibrous regions were observed in the

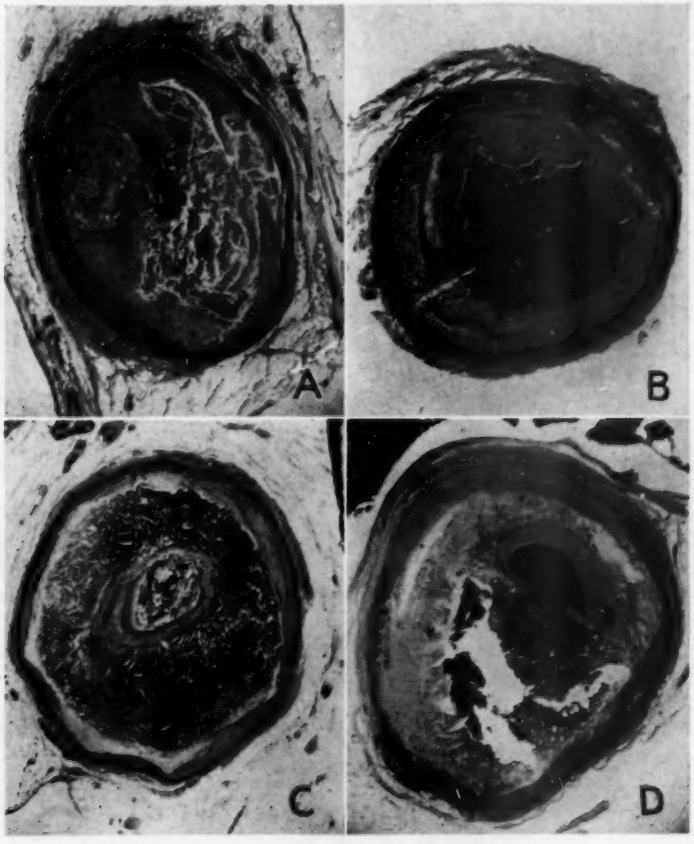

Fig. 6.—Exceptions in group 2. Atheromatosis in young men. *A* (case 20), organized thrombus in lumen; atheromatous "abscess" occupying most of vessel. *B* (same case), terminal thrombosis in fibrosed vessel. *C* (case 21), canalized lumen surrounded by atheroma. *D* (same case), terminal rupture of vessel into atheromatous "abscess."

myocardium near the apex and along the junction of the wall and the septum in the region of distribution of the left coronary artery. The orifice of the right coronary artery was small. The descending branch of the left coronary artery was almost completely obliterated except for a pinpoint-sized opening about 2 cm. from the orifice, with some calcification. The lumen was generally somewhat narrowed. The circumflex branch was of relatively large caliber, with patches

of thickening of the walls. The right coronary artery was rather small, with marked thickening of the wall and narrowing of the lumen 1.5 cm. from the orifice. The aortic sclerosis was advanced, of nodular type with scarring in the arch and thoracic regions together with plaques of lime salts, and with many high atheromatous foci in the abdominal portion of the vessel. Figure 5 *I* shows *a large atheromatous process almost surrounding the lumen, which is very small.*

EXCEPTIONS IN GROUP 2 (FIG. 6)

CASE 20.—A man, aged 37, an instructor in an automobile school, had been well except for attacks of indigestion. He had been an intermittent drinker. On his return from overseeing the registration of a student, he said that he did not feel well about the heart and had had to vomit at the registry. He went out to a restaurant, sat down in a chair and collapsed, dying immediately. The heart weighed 370 Gm. There was hypertrophy of the left ventricle. No infarction was seen. In the left coronary artery, beginning 0.6 cm. from the orifice, was a clot which extended 1 cm. Below this the wall of the vessel was thickened and almost completely obliterated for 1.5 cm. In the circumflex branch were found minor yellow opaque patches of thickening. In the midregion of the right coronary artery the wall was thickened almost to obliteration. The aorta was not described. Figure 6 *A* shows *a very large atheromatous focus, but the site of the lumen (left) is occupied by organizing tissue replacing evidently a thrombus. In a section at a higher level (B) the thrombus which caused death in a second attack is shown.*

CASE 21.—A man, 38 years of age, a veteran being compensated for a cardiac condition, collapsed while wading in shallow water. Autopsy disclosed no evidence of drowning. The heart weighed 610 Gm. An old infarction and thinning of the septum and adjacent left ventricular wall running upward from the apex 8.5 cm. and 5 cm. wide were found. The descending branch of the left coronary artery was grossly occluded 2 cm. from the orifice, with some calcification. The circumflex branch was also occluded 2 cm. from the origin. Beyond these regions of occlusion the vessel was filled with blood. In the right coronary artery there was thickening of the wall with a small lumen free from clot. In the aorta were found a series of small white scars in the descending arch and about the orifices of the branches, notably the intercostal. Calcified plaques occurred in the upper abdominal part of the vessel with yellow opaque deposits scattered in the part below. Figure 6 *C* shows *a large atheromatous focus encircling a central fibrous layer about what was the lumen. At the site of the lumen occur a series of canaliculi, apparently resulting from an old organized thrombus. At a different level (D) there is rupture from the vascular lumen into an atheromatous pocket.*

It is evident in each of these exceptions to the rule, occurring in young men, that earlier thrombosis was responsible for the older age reaction shown.

SUMMARY OF OBSERVATIONS IN GROUP 2

The formation of an atheromatous cavity or "abscess" begins by the laying down of masses of lipoid cells with a minimal amount of supporting fibrous tissue. The partitions between the cells in many cases are slender strands of reticulum (fig. 7 *A*). These massive accumulations of cells are dependent on imbibition for their nutrition, even when, in some cases, vasa vasorum have penetrated through the media. As

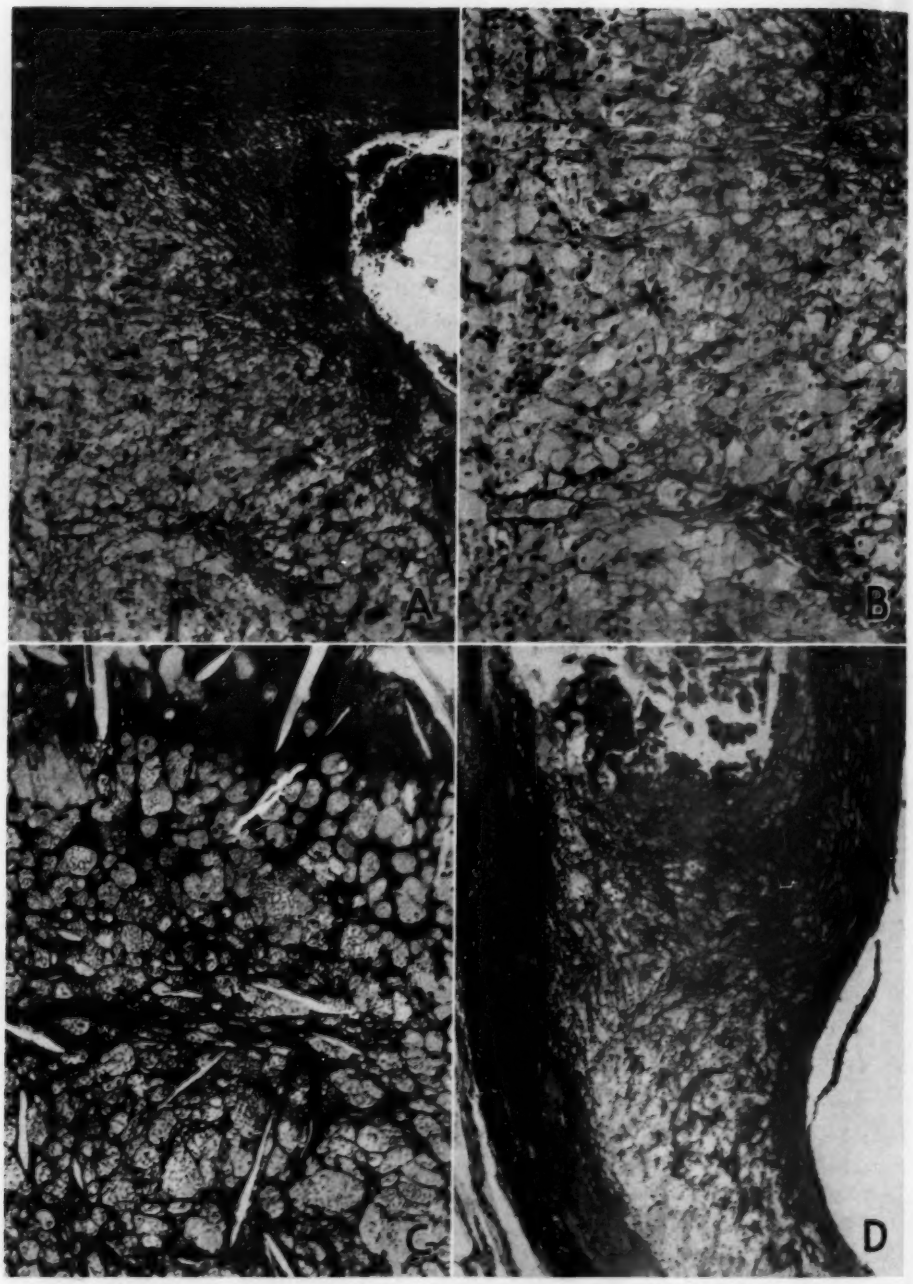

Fig. 7.—Human coronary arteries showing evolution of atheromatous "abscess:" *A*, lipoid cell masses near lumen; × 110. *B*, detail of lipoid cell masses; × 175. *C*, necrotic lipoid cells with splitting of lipoid esters; × 200. *D*, atheromatous "abscess;" × 76.

a result of the hazard to the nutritive supply, necrosis tends to occur (fig. 7 *C*). This is associated with the splitting of the esters contained within the cells, and cholesterol crystals are formed. The space occupied by the dead cells is converted into a cavity filled with living and necrotic cells, detritus, cholesterol crystals and fluid (fig. 7 *D*). Such an accumulation was given the name of atheromatous "abscess" from its gross appearance. The lesion is not, however, inflammatory in any sense. Striking is the constant absence of bacteria and of inflammatory cells from such a focus. The protective properties of cholesterol are probably responsible for this constant absence of infection.

The standard cause of death in this group is the rupture of an atheromatous cavity into the lumen, secondary thrombus formation occurring in most of the instances (cases 13, 15, 16, 17 and 18; fig. 5 *C, E, F, G* and *H*). Or rupture may occur from the lumen into an atheromatous focus (case 14; fig. 5 *D*). Death may also arise from coronary insufficiency (case 19; fig. 5 *I*).

CONCLUSIONS

From this study of coronary sclerosis certain facts appear: 1. Atherosclerosis is a disease and not the inevitable consequence of age, since it appears in the young and may be highly selective in its localization. 2. The characteristic lesion in youth is a fibrosis associated with the presence of lipoid cells, which do not accumulate in large aggregations, because of the growth of the fibrous tissue. 3. The characteristic lesion at older ages is the accumulation of large collections of lipoid cells with minimal connective tissue support. As a result of poor nutrition, massive necrosis occurs, giving rise to so-called atheromatous "abscesses." 4. The standard cause of death in the young is thrombosis following subendothelial necrosis which extends to the endothelium. 5. The standard cause of death in the older group is the rupture of an atheromatous "abscess" into the lumen, usually followed by thrombosis. 6. The process is primary in the intima; stresses favor the localization of the lesions; morphologic lesions in the elastica and media occur secondarily. 7. The disease is not inflammatory in origin.

II. EXPERIMENTAL ATHEROSCLEROSIS IN THE RABBIT

SUITABILITY OF RABBITS FOR THE PRODUCTION OF EXPERIMENTAL ATHEROSCLEROSIS

In the period from 1903, when Josué [4] claimed to have produced medial arteriosclerosis in rabbits by the use of epinephrine, up to 1912, a series of papers was published by various authors describing the

4. Josué, O.: Compt. rend. Soc. de biol. **55**:1374, 1903.

occurrence of spontaneous sclerosis in the aortae of normal rabbits, the highest occurrence being 34.6 per cent recorded by Miles and Johnstone,[5] and 52 per cent, by Levin and Larkin.[6] The lesions described, however, were almost without exception of medial origin or limited to the media, and Miles and Johnstone's photomicrographs, all of medial lesions, show calcification in 3 out of 4 illustrations, while Levin and Larkin's [7] illustrations show medial lesions and calcification in 3 of 5 normal animals. These statistics were used to controvert claims that the type of sclerosis appearing in the media in experiments with epinephrine was due to the epinephrine used. Levin and Larkin concluded: "It would seem, therefore, that the rabbit is not a suitable animal for the study of experimental arteriosclerosis."

The only resemblance of the arteriosclerotic lesions described by Miles and Johnstone and Levin and Larkin, or produced by epinephrine, to any form of human arteriosclerosis is to the so-called Mönckeberg type found in the peripheral arteries and rarely in the aorta or visceral arteries. Mönckeberg regards this as independent of true arteriosclerosis, since there are slight changes in the intima and extreme changes in the media. It can be agreed that for the experimental production of this type of sclerosis the rabbit is not a suitable animal.

In viosterol sclerosis, the viosterol apparently serves as a menstruum only, the radiant energy which it carries being responsible for the arterial lesions. These lesions are medial, as are the spontaneous and epinephrine-caused scleroses discussed, and have little or no relation to those of human atherosclerosis.

The common type of human arteriosclerosis is *atherosclerosis,* which makes up at least 95 per cent of sclerotic lesions of human visceral arteries (syphilis excluded), and is primarily an intimal process, independent of the uncommon Mönckeberg type. The intimal form of sclerosis is rare in younger rabbits, such as are used for laboratory work. Clarkson and Newburgh [8] cited records of 3,024 rabbits reported on by several workers in experimental medicine with 10 possible examples (0.33 per cent) of spontaneous sclerosis of the aorta which might be of the atherosclerotic type. If by experimental methods one can produce over 90 per cent of positive atherosclerotic results, it is evident that discussion of the possibility of spontaneous processes invalidating the results is futile. Moreover, if lesions are produced which cover a large part of the aorta in contrast to the relatively minute lesions described so rarely in normal animals, the importance of possible spontaneous lesions becomes minimal.

---

5. Miles, A. B., and Johnstone, O. P.: J. A. M. A. **49**:1173, 1907.
6. Levin, I., and Larkin, J. H.: Proc. Soc. Exper. Biol. & Med. **7**:109, 1909.
7. Levin, I., and Larkin, J. H.: J. Exper. Med. **13**:24, 1911.
8. Clarkson, S., and Newburgh, L. H.: Arch. Int. Med. **31**:653, 1923.

Age to Which Rabbits Live.—The natural longevity of rabbits is a subject on which exact data are difficult to obtain. Breeders continue to use animals up to 6 years of age and even beyond, but their records are often unsatisfactory. Inquiry at biologic institutes brought no data except the record of a single animal, which was killed because senile, at 8½ years, by Dr. William E. Castle of the Bussey Institute of Harvard University. The animals used in the present research had reached a maximum age of 17 months when killed. There is an apparent relation between the single years of a rabbit's life and the decades of a human life. Viewed from this standpoint our oldest animals were comparatively only in their "teens."

CHOLESTEROL

According to Schoenheimer,[9] who has carried out extensive studies on the sterols, cholesterol is one of the most complicated substances in the animal body. Apart from ergosterol, which is found in small amounts, it is the only sterol found in the animal body, and does not occur in nature except in animal bodies. It is a relatively insoluble substance which is highly resistant to the action of enzymes, whether of bacterial, vegetable or animal origin, and is the only sterol (in addition to viosterol) which is absorbable. The many plant sterols, most of which have the same chemical formula as cholesterol, $C_{27}H_{46}O$, differ from it in molecular arrangement. Their nonabsorbability is apparently dependent on these differences. The sterols unite with fatty acids to form esters and tend to be associated with the glycerol fats. In mixtures with fats and in extracts of tissues by fat solvents the sterols are found in the unsaponifiable residue. Cholesterol is synthesized by the animal body, notably among the herbivora, but the principal human provision of this material comes from ingestion of the products of herbivora. Egg, milk and pork fats are the main sources of supply.

Cholesterol is present in every animal cell. Of its cell functions Starling[10] said: "In view of the great stability of this substance when exposed to the ordinary mechanisms of chemical change in the body, it seems probable that the part played by cholesterol is that of a framework or skeleton, in the interstices of which the more labile of the constituents of the protoplasm undergo the cycle of changes which make up the phenomena of life." The cholesterol which is secreted with the bile assists in the absorption of fats from the intestine and is itself largely resorbed. Cholesterol is believed to be responsible for the impermeability of cells to certain toxic agents, is the important agent resisting hemolysis, and is supposed to confer protective properties on cells.

9. Schoenheimer, R.: Science **74**:580, 1931.

10. Starling, E. H.: Principles of Physiology, Philadelphia, Lea & Febiger, 1930, p. 42.

That it highly resists infection is manifest in the constant absence of infection from so-called atheromatous "abscesses." It tends to accumulate in the animal body, i. e., to be stored, and its avenues of excretion are limited. Its metabolism appears to be influenced by thyroid secretion.

All animals must have a metabolic system caring for the absorption and distribution of cholesterol to satisfy the requirements of their cells, and the herbivora at least synthesize the substance. Since herbivora do not naturally ingest cholesterol their threshold of tolerance is low. It is therefore possible to overload their cholesterol metabolic systems more readily than is true with the carnivora, whose diet includes cholesterol. The limitations of time demand the experimental production, in a short period, of lesions that require a lifetime for natural production.

EXPERIMENTAL METHODS AND RESULTS

The experiments reported here were started with rabbits 5 months old, some of which were kept in reserve for replacements. Cholesterol was fed by catheter for a maximum period of seven months. Some rabbits died before the end of the feeding period. At the end of this period all of the surviving animals except 4 were killed. These were allowed to live for five months after feeding ceased. For the first four months of the feeding period starch paste was used as a menstruum, the pure cholesterol being finely powdered before suspension. For the remaining three months sunflower seed oil was substituted as a menstruum, the cholesterol being dissolved (1 Gm. to 20 cc.) in warm oil. The dosage was gradually increased from 0.2 Gm. to a maximum of 1.4 Gm. daily, six times a week, with intermissions if animals lost weight or were ill. A limit of tolerance at about 1 Gm. of cholesterol per diem was established. Beyond this animals tended to develop diarrhea and roughness of coat, and some died. Control animals receiving equal amounts of sunflower seed oil without cholesterol were not affected.

The results in cholesterol-fed animals were, in general, more marked than the lesions described in the literature. As measured by aortic manifestations they were as follows:

Four rabbits exhibited advanced atherosclerosis throughout the aorta with extension to its branches. Of these, 1 had been allowed to live five months following cholesterol feeding.

In 8 rabbits there were continuous lesions throughout the arch with extension to its branches and through the thoracic portion of the vessel, and there were scattered lesions below this portion. Of these, 1 had lived five months following cholesterol feeding.

In 7 rabbits continuous lesions were present in the arch with scattered foci below. Two of these had lived five months following cholesterol feeding.

In 6 rabbits there were no continuous lesions, but scattered small lesions of atherosclerosis were found.

In 2 rabbits which were killed during the period of starch and cholesterol feeding, the aortae were normal.

Five normal controls fed starch paste and later oil, 5 controls receiving insulin and 4 controls receiving alcohol showed normal aortae. In an alcohol-fed control there were 2 *medial* foci of sclerosis in the arch, 0.3 cm. in diameter.

One rabbit killed for observation in the early period, when starch paste was used as a menstruum, died at too early a date for the development of sclerosis. Even including this animal, in 25 of 27 rabbits fed cholesterol, or 92.6 per cent, atherosclerosis was produced. In 14 controls no atherosclerosis was found. In 1 control medial sclerosis was present.

Two interesting elements appear in these results. Though large amounts of cholesterol were fed equally to many animals, the gross end-results varied from small scattered lesions to extreme processes that included almost the whole of the aorta, parts of its branches, and visceral arteries, and were associated with evident hypertrophy of the heart. This variation in susceptibility is perhaps comparable to the idiosyncrasy toward atherosclerosis exhibited by human beings, who may die in the twenties from coronary sclerosis or may live to the age of 70 or 80 and show little arteriosclerosis. The absence of atherosclerosis in controls that received sunflower seed oil (without cholesterol) in equal amounts with cholesterol-fed animals is in accordance with the finding of Schoenheimer and his associates that phytosterols are not absorbable.

THE LESIONS

It should be kept in mind that the experimental lesions present, in general, earlier stages in the process than are seen in most human material. However, progress in the study of arteriosclerosis, as is true in other diseases, will come from the reproduction and observation of early lesions. The illustrations from experimental lesions in figures 8 to 14 inclusive are from various vessels, as indicated.

Imbibition of Lipoid Esters.—The first manifestation of vascular lipoidosis is the appearance of the lipoid in spaces beneath the endothelium of the blood vessels. Whether this is properly a matter of imbibition or the result of secretory activity of the endothelial cells is not known. The endothelium gives no evidence of disturbance, but is

lifted mechanically as the deposit occurs, together with the inner elastic lamina in some vessels. Some observers have reported the presence of fine droplets of lipoid in the endothelial cells before the appearance of cholesterol beneath the endothelium. Figure 8 *A* is a cross-section of a

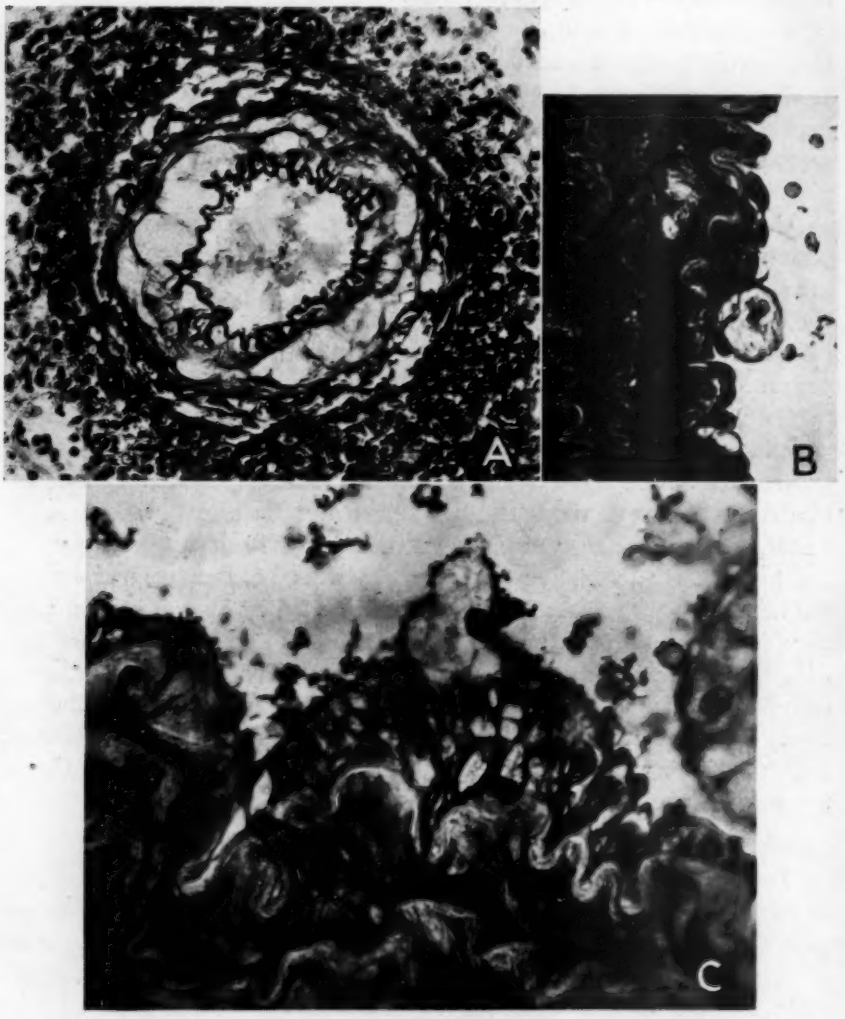

Fig. 8.—*A*, splenic arteriole of rabbit; × 300; lipoidosis. *B*, innominate artery of rabbit; lipoid cell adhering to wall. *C*, carotid artery of rabbit; × 350; lipoid macrophage invading (?) wall. Note proliferation of subendothelial connective tissue at this point.

splenic artery, in which the internal elastic lamina is seen to be carried up with the endothelial layer.

The Macrophage—The Lipoid Cell.—Early in the evolution of the vascular processes appear cells which engulf the cholesterol esters and give rise to the most characteristic element in human or in experimental sclerosis, i. e., the large macrophage loaded with lipoid esters in fine or coarse droplets. The source of these cells is in question. They are not resting wandering tissue cells (histiocytes) which emigrate to the place where foreign material has accumulated. They either arise locally from the subendothelial layer or are invaders from the blood stream (monocytes). Figure 8*B* shows one of these cells attached to the wall of an innominate artery at a point where there is little evidence

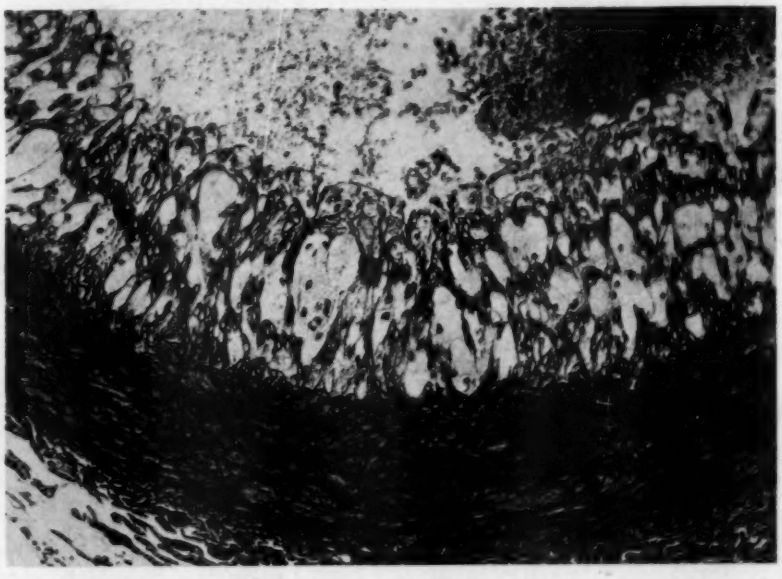

Fig. 9.—Carotid artery of rabbit; × 140; festooned masses of subendothelial connective tissue cells enclosing lipoid macrophages.

of lipoidosis. In figure 8*C* a large macrophage is apparently invading or leaving the wall at a point where lipoidosis is beginning. These cells are found locally, in the blood stream and in the splenic sinuses.

Massing of Lipoid Cells.—As the disease progresses the lipoid cells become massed in the subendothelial connective tissue. In the experimental form the layers of cells may be multiplied into hillocks which distort the lumen of the vessel. The cells are separated by delicate partitions of connective tissue, though more than one cell may occupy a compartment in the connective tissue. The picture when cell groups are excessive in the rapid early experimental process is shown in figure 9. The slower standard experimental lesion is illustrated in figure 10*A*. The cells are large globular structures, and sections are unlikely to

include the nucleus in each cell of a group. Figure 10 *B* shows lipoid cells grouped beneath the endothelium in a human coronary artery.

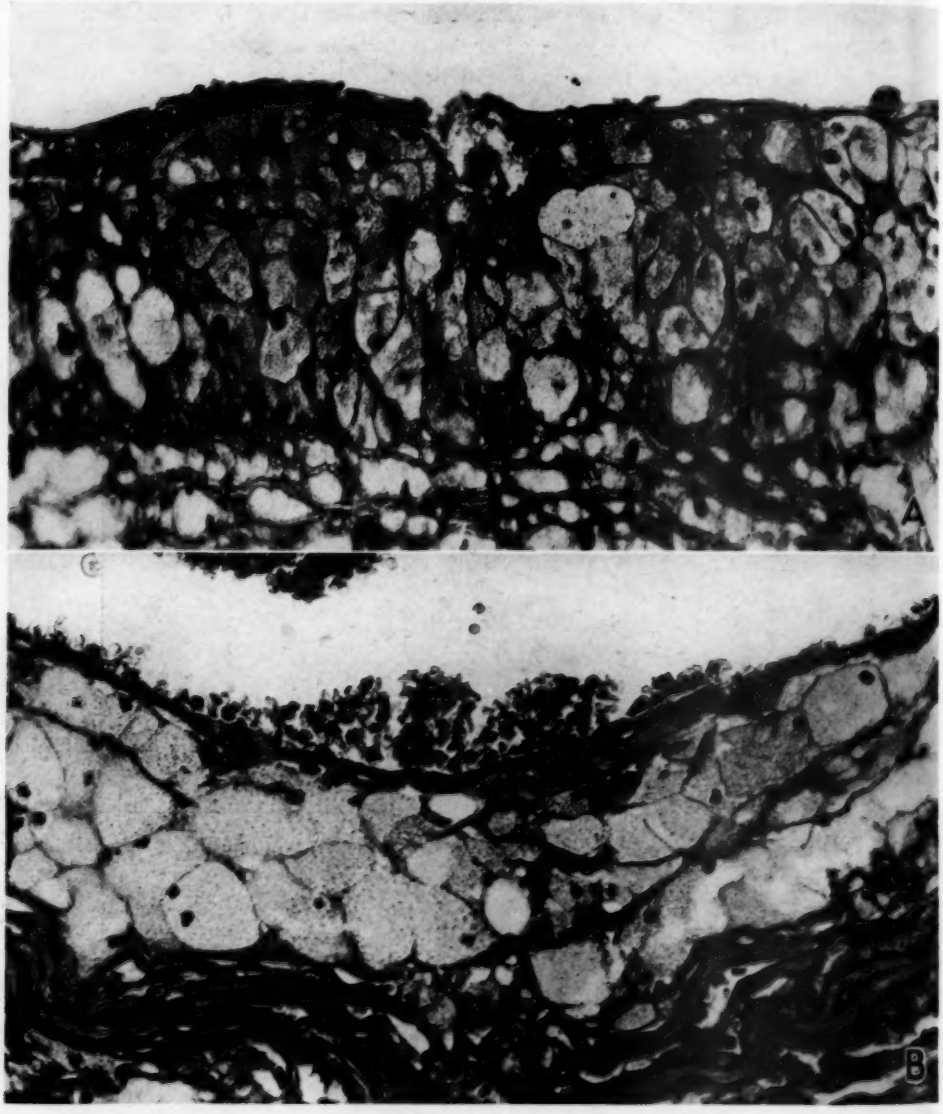

Fig. 10.—*A*, innominate artery of rabbit; × 300; subendothelial masses of lipoid cells. *B*, human coronary artery; × 350; lipoid cells beneath endothelium.

Deep Invasion by Lipoid Cells.—As the process ages it is common to find deeper invasion by some of the lipoid cells as fibrosis of the

inner layers takes place. This is illustrated in figure 11 *A*, while figure 11 *B* shows focal invasion of the media in a human coronary artery.

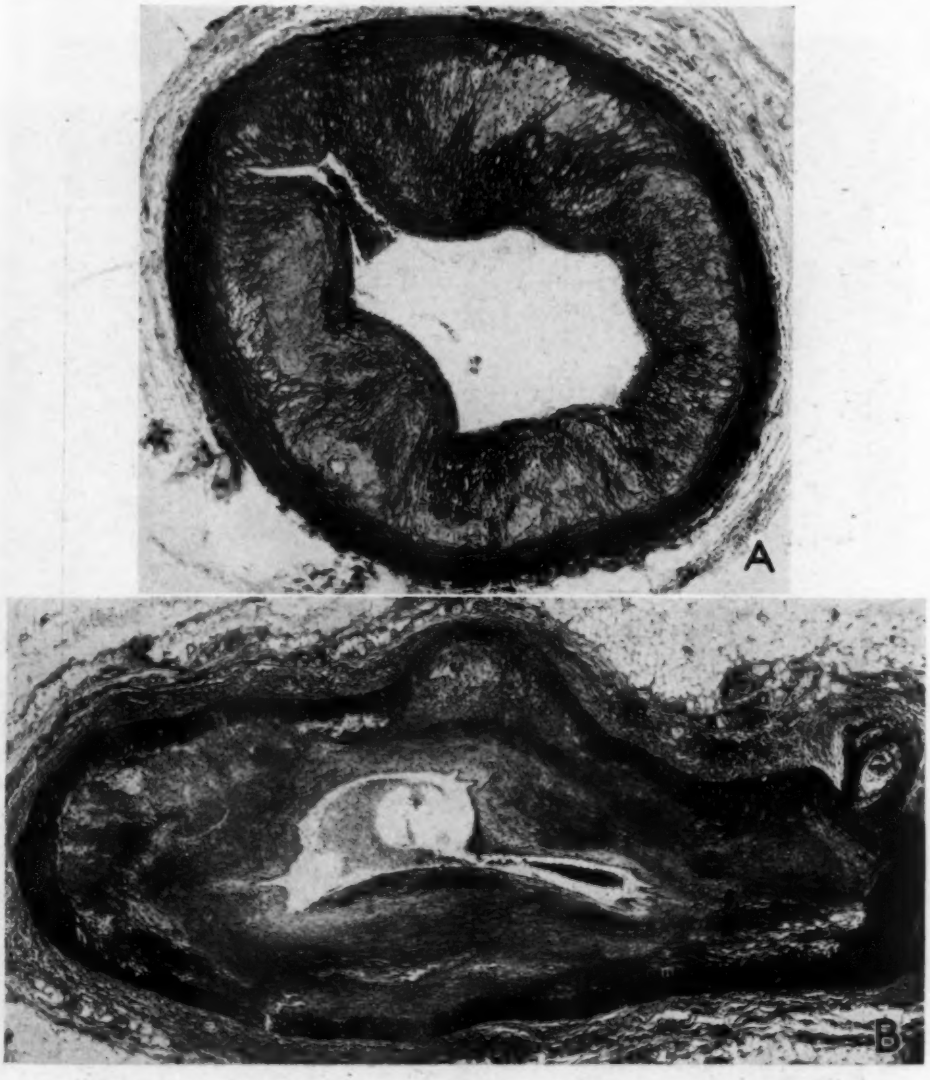

Fig. 11.—*A*, carotid artery of rabbit; × 50; internal fibrosis; deeper, lipoid cells. *B*, human coronary artery; × 23; focal invasion of media by lipoid cells.

Splitting of Lipoid Esters.—When lipoid cells accumulate, even in isolated groups, necrosis of the cells tends to occur. The early stages are marked by the breaking down of the cytoplasm and the fusing of the esters, which have existed in fine droplets, into larger drops. This

is followed by the splitting of the esters and the freeing of cholesterol in crystal form. This picture is found in the rabbit lesions usually in regions where larger accumulations of lipoid cells are undergoing

Fig. 12.—Innominate artery of rabbit; × 100; atheromatous "abscess."

fibrosis, and in advance of the growing fibroblastic tissue. It is not a very common finding. In human coronary arteries in the young, deposits of cholesterol crystals are met with, usually in small groups, where small isolated collections of lipoid cells have undergone necrosis.

A rare lesion in the rabbit is the atherosclerotic cavity or "abscess." Antischkow has never produced it and it is not reported in the literature. It probably resulted in my series from the introduction of very large

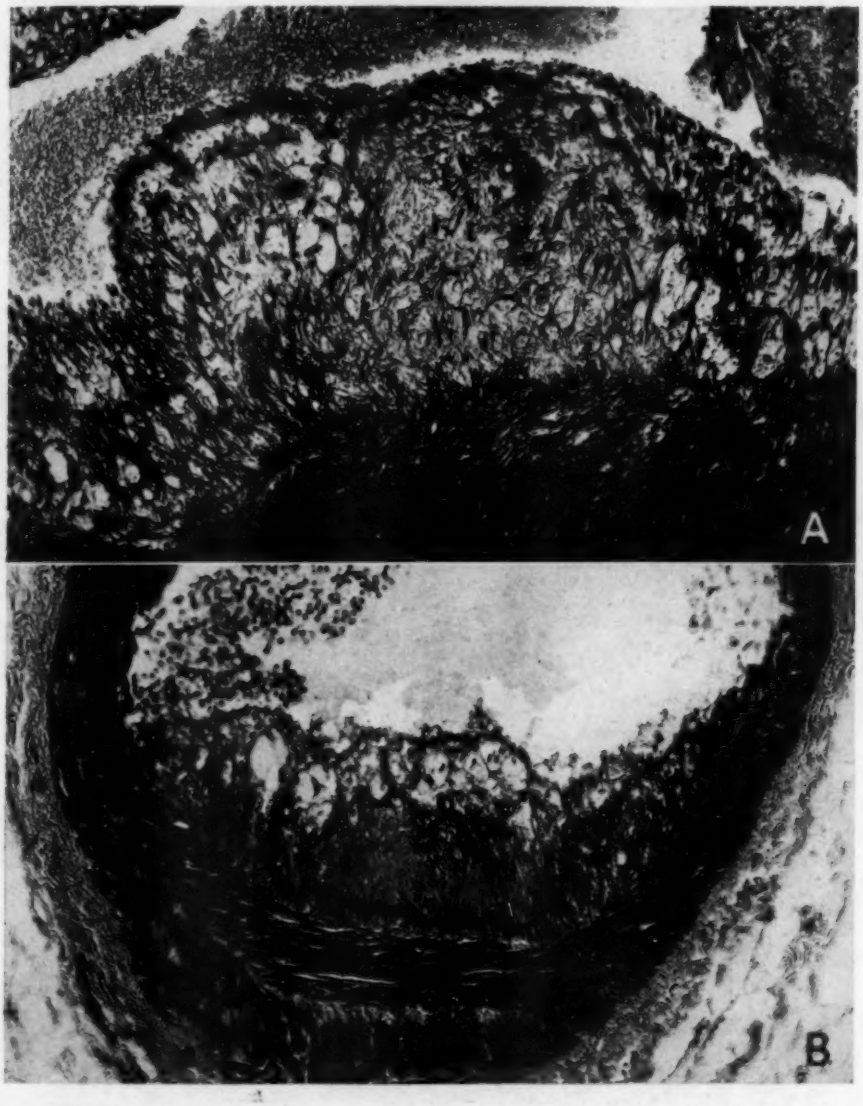

Fig. 13.—*A*, innominate artery of rabbit; × 100; beginning fibrosis in mid-portion of nodule of lipoid cells, before formation of dense fibrous tissue. *B*, human coronary artery in case 3; × 130; fibrosis replacing lipoid cells.

amounts of cholesterol into a susceptible animal. Its appearance (figure 12) corresponds closely, on a smaller scale, to the human lesion illustrated in figure 7 *D*.

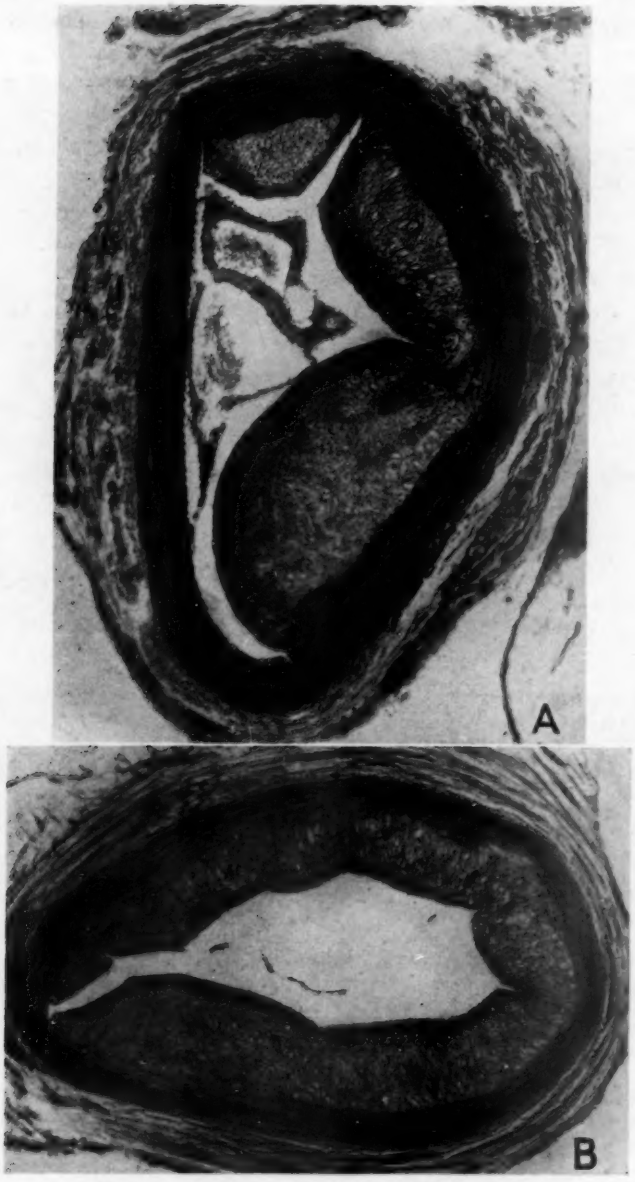

Fig. 14.—*A*, subclavian artery of rabbit; × 50; eccentric fibrosis. *B*, subclavian artery of rabbit; × 21; concentric fibrosis.

Fibrosis.—The standard progressive change in the rabbit is fibrosis. When the accumulation of lipoid cells has reached a certain degree, young fibroblasts appear and replace the cells. This replacement is total, including the lipoid cells, their contents and the supporting tissue. It is unaccompanied in general by the splitting of the esters, though occasionally small deposits of cholesterol crystals are found. An early stage of fibrosis is seen in figure 13 *A*. A central island of fibroblastic tissue is invading and replacing the new lipoid tissue. Figure 13 *B*, a comparable picture, is from a branch of the human left coronary artery in case 3. The human lesion is older, and the mass of tissue in the center is fibrous, but fibroblastic cells are active on the sides.

In both rabbit and man the formation of fibrous tissue is more frequently diffuse than local, the delicate strands between the lipoid cells becoming thicker as the lipoid cells disappear.

The result of fibrosis, which tends to progress pari passu with the occurrence of lipoid cells, is the formation of fibrous masses distorting and narrowing the lumen of the vessel. Eccentric fibrosis is illustrated in figure 14 *A* and concentric fibrosis in figure 14 *B*. The fibrous tissue in the experimental lesions that I describe was largely limited to the intima, but Wolkoff [2c] described, with reproductions, advanced lesions in which the fibrous tissue had invaded the media in rabbits allowed to live for years following the cessation of cholesterol feeding.

III. COMPARISON OF HUMAN AND EXPERIMENTAL RABBIT ATHEROSCLEROSIS IN THE CORONARY ARTERIES

(All of the illustrations which follow are from coronary arteries, save figure 21.)

The lesions of human coronary sclerosis reported in part I were observed in advanced cases which terminated in death. In the secondary branches of the coronary arteries from some of these cases early lesions (e. g., fig. 13 *B*) were found. In general, however, the human process is of so slow evolution that initial or early processes are hard to find. Search for the earliest processes was finally successful in the left coronary arteries of infants who died in the early days of life from congenital heart disease. The burden thrown on the myocardium in its effort to keep up a circulation under the handicap of developmental faults causes unusual stresses on the coronary arteries, with resulting lesions. These have supplied illustrations of the earliest natural processes found.

Figure 15 *A* from the coronary artery of a rabbit illustrates lipoidosis, which is the first stage in the process. In the larger vessel, the descending branch of the left coronary artery, there is a deposit of lipoid under the endothelium at one point; a more massive deposit is shown in the two branches above.

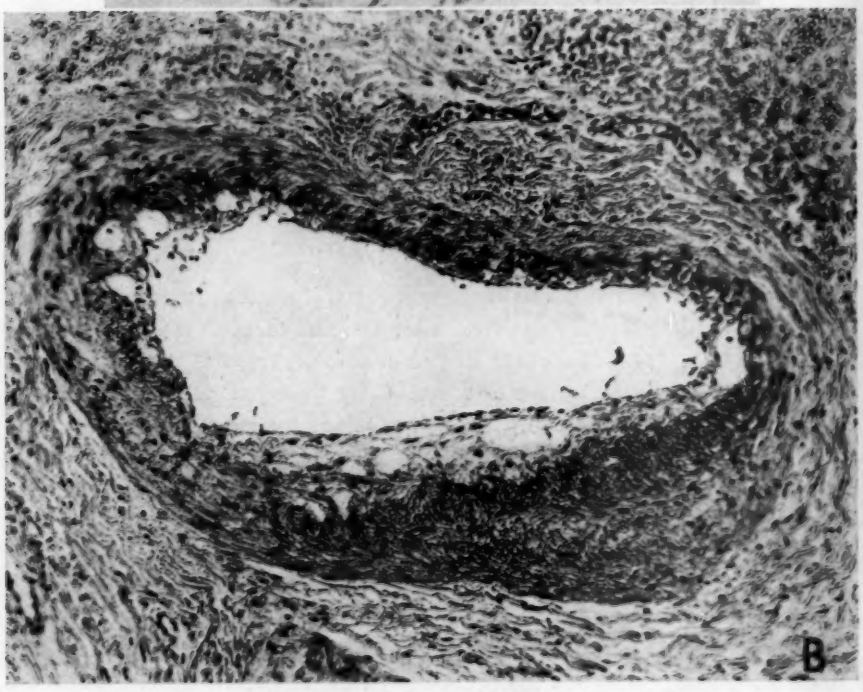

Fig. 15.—*A*, coronary artery of rabbit; × 120; lipoidosis, focal in main vessel and general in branches. *B*, human coronary artery at 3 days of age; × 150; lipoidosis and lipoid cells.

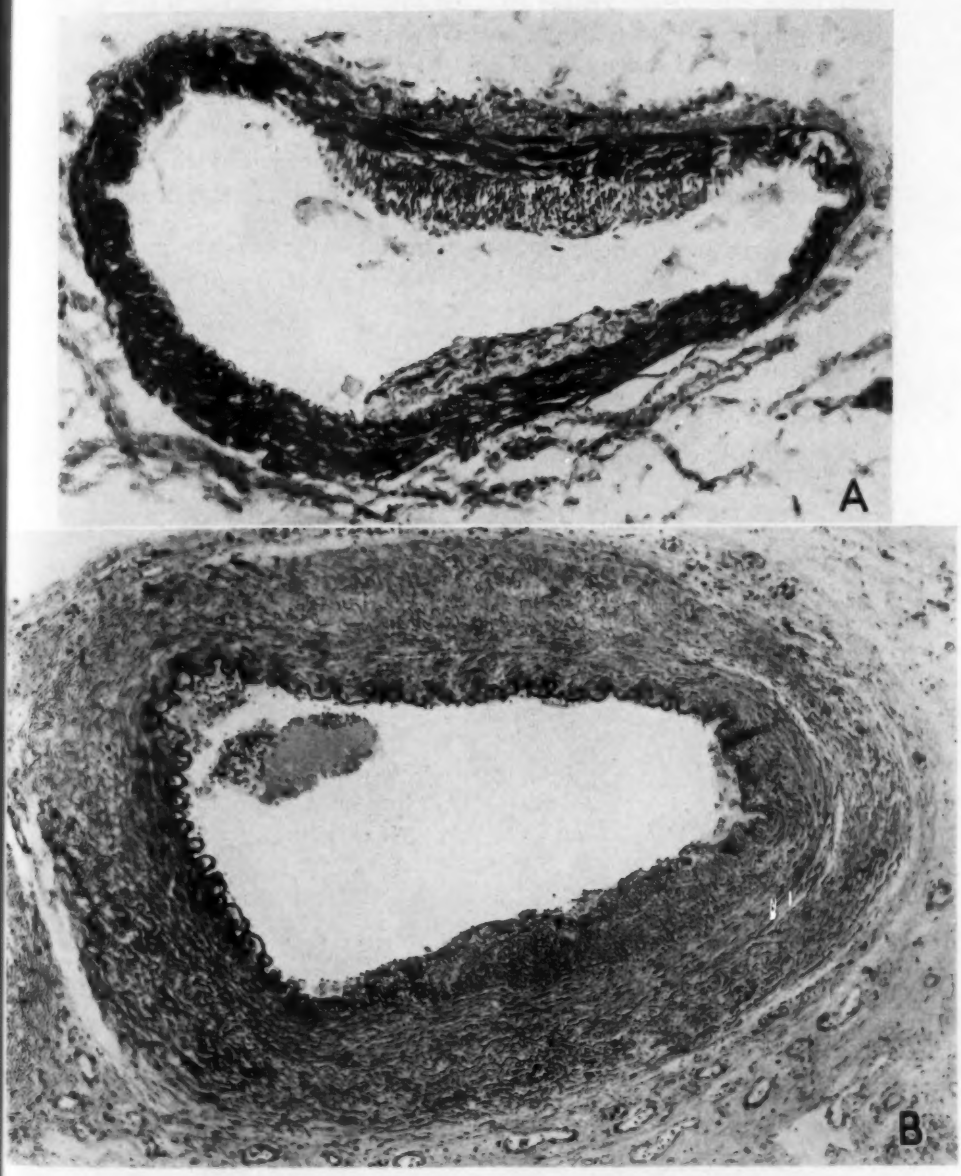

Fig. 16.—*A*, coronary artery of rabbit; × 120; early lesion with lipoid cells below and early fibrosis above. *B*, human coronary artery at 33 days of age; × 85; early fibrosis; elastica largely absent under lesion.

Figure 15 *B* is from the left coronary artery of a blue baby who died three days after birth. At postmortem examination there was found pulmonary and tricuspid atresia with cor triloculare. The vessel shows diffuse subendothelial lipoidosis, and lipoid cells are present at each end of the affected region. In figure 16 *A* from the coronary artery of a rabbit two stages in the evolution of the characteristic lesion are seen. On the lower side is a relatively early process in which lipoid cells are moderately abundant. On the opposite surface is a cellular

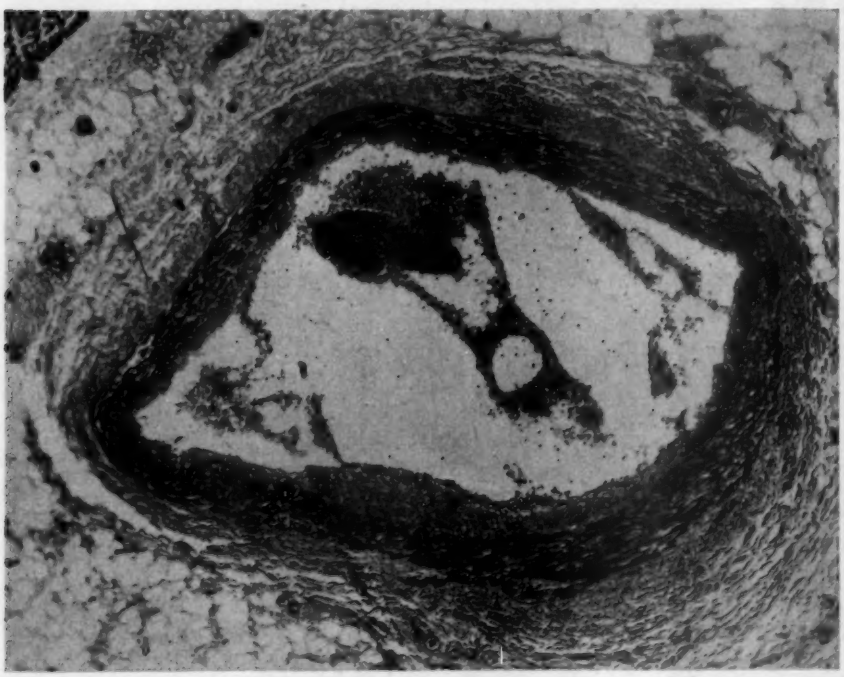

Fig. 17.—Human coronary artery at 14 years of age; ×60; formation of irregular buffer layer.

fibrous lesion resembling closely that seen in the buffer layer of the normal coronary artery. Figure 16 *B* is from the left coronary artery of an infant with mongolism and also an imperforate anus which was successfully operated on. Death occurred thirty-three days after birth. Postmortem examination disclosed defective auricular and ventricular septums and a patent ductus arteriosus. The figure shows a subendothelial fibrous lesion along the lower edge of the lumen. The prominent internal elastic lamina is lost under the new tissue in the right lower quadrant. Figure 17, which is from a branch of the normal left coronary artery of a boy aged 14, reveals the irregular distribution of the subendothelial tissue in the buffer layer, which has not yet reached the

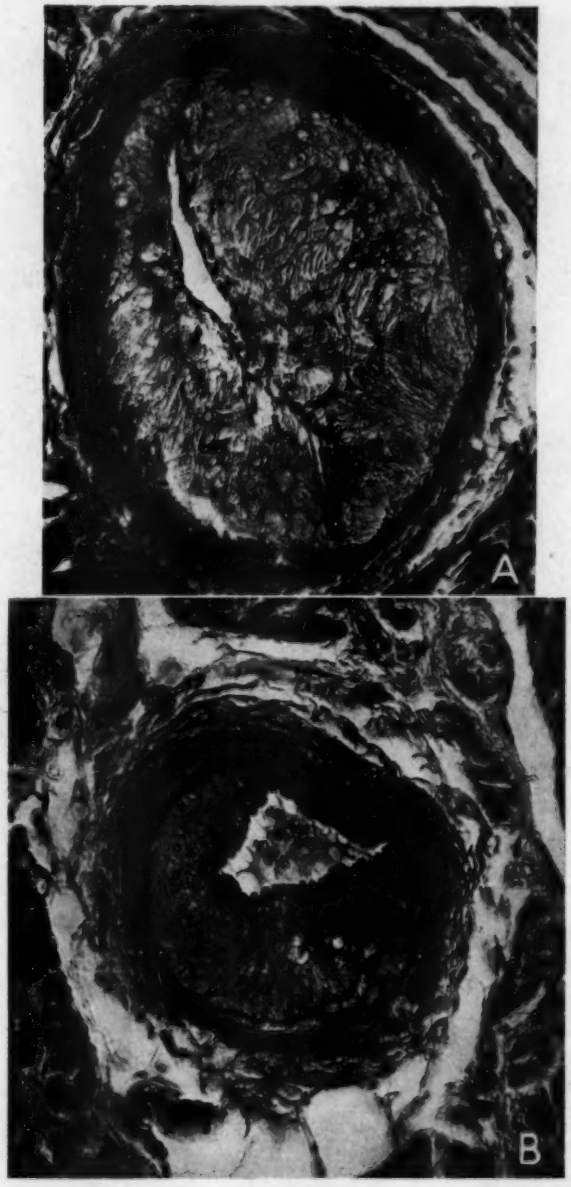

Fig. 18.—*A*, coronary artery of rabbit; ×300; lipoidosis with concentric fibrosis. *B*, coronary artery of rabbit; ×300; advanced fibrosis in small branch with intact, though flattened, elastica.

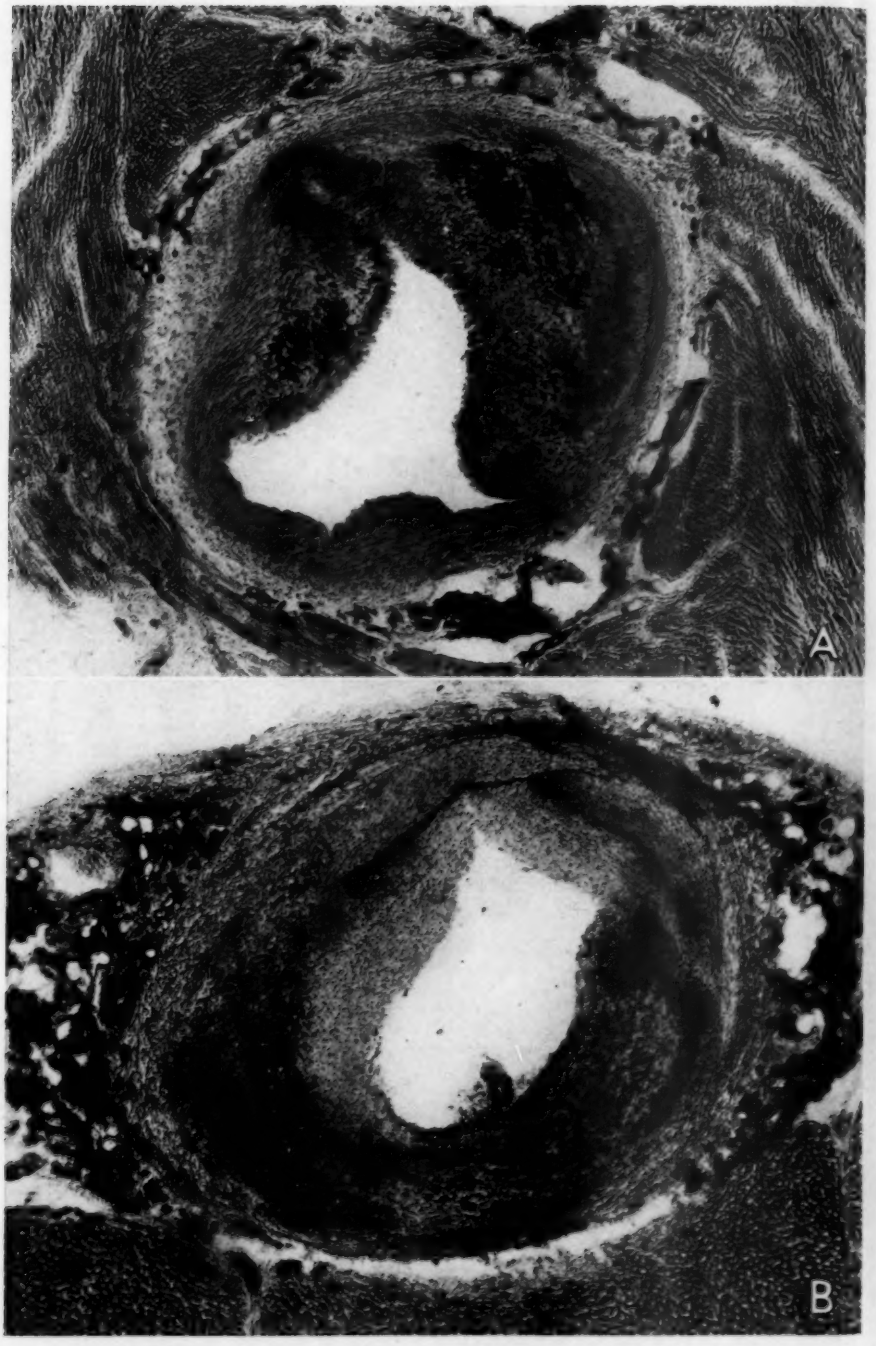

Fig. 19.—*A*, coronary artery of rabbit; × 60; advanced fibrosis with secondary fatty changes. *B*, human coronary artery; × 30; frozen section stained with sudan IV. Compare with *A*.

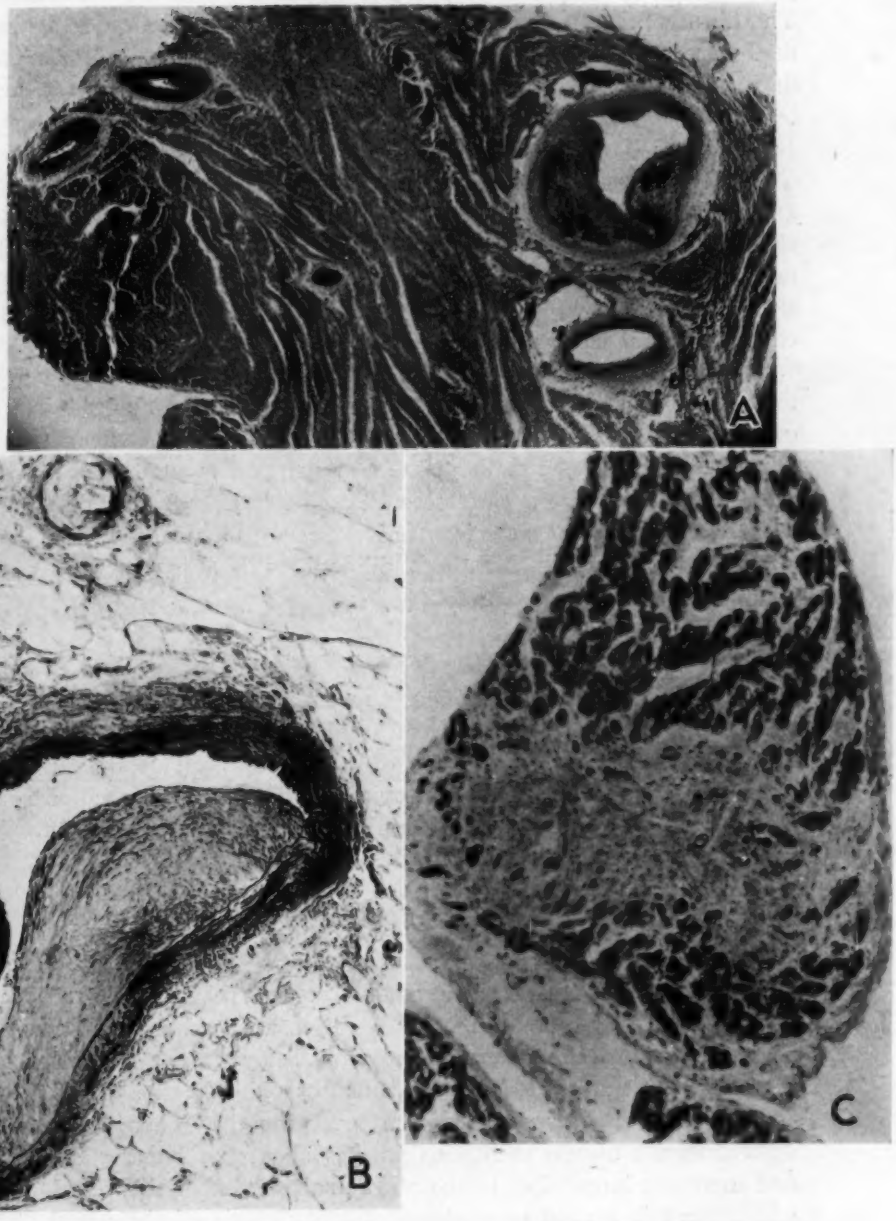

Fig. 20.—*A*, heart of rabbit; × 17; frozen section, stained with sudan IV; late lesion in main vessel; lipoidosis of branches. *B*, coronary artery of rabbit; × 120; eccentric fibrosis in descending branch; narrowing of lumen of auricular branch above. *C*, section of cardiac auricular wall of rabbit; × 150; myocardial atrophy and repair.

perfection of the layer of regular thickness found in the main vessel. The fibrous tissue making up this layer corresponds in its details with that seen in the upper lesion in figure 16 *A*. A concentric lesion producing marked narrowing of the lumen, but still rich in lipoids, may be seen in figure 18 *A* and an eccentric, more fibrous process in figure 18 *B*.

As the fibrous tissue ages secondary fatty metamorphoses arise, and necrosis of the intimal tissue may occur. In figure 19 *A* and *B* are shown frozen sections stained with sudan IV and hematoxylin. The rabbit lesion (*A*) exhibits an eccentric fibrosis with secondary fatty changes. The human lesion (*B*) is more advanced, but the fundamental character of the lesions is similar in all respects.

The cyclic character of the atherosclerotic process is suggested by the occurrence of comparatively recent lipoidosis in the smaller branches of the left coronary artery of a rabbit (fig. 20 *A*) in contrast to the advanced lesion in the main vessel, as illustrated in figure 19 *A*. This rabbit had received no cholesterol for five months before its death. The lipoidosis in the splenic arteriole seen in figure 8 *A* was from another animal which had been allowed to live five months after cholesterol feeding had ceased.

SECONDARY EFFECTS

A common end-result of human coronary sclerosis is focal atrophy of the heart muscle and replacement fibrosis (so-called chronic myocarditis). In figure 20 *B* fibrosis of a larger branch of the coronary artery of a rabbit is seen with marked narrowing of the auricular branch above it. Section of the auricular wall disclosed focal atrophy of the heart muscle and repair (fig. 20 *C*).

VARIATION IN AORTIC LESIONS

Three rabbit hearts and aortae are shown in figure 21. The central heart and aorta were obtained from a normal rabbit of certified age killed when 7 years and 1 month old, i. e., approaching senility. The aorta shows no lesions. For comparison, below it, are the heart and aorta of rabbit 29, killed when 12 months old, after being fed 128.8 Gm. of cholesterol over a period of seven months. There is a diffuse atherosclerosis of the arch with patches about the intercostal orifices and there are larger foci in the abdominal portion of the vessel. In a word, there is a mild to moderate atherosclerosis of the vessel. The upper heart and aorta are from rabbit 32, which was found dead. It had been fed 1.4 Gm. of cholesterol on the day before and had ingested a total amount of 113.8 Gm. of cholesterol. When this rabbit was found its fur was soiled with a diarrheal discharge. In the vessel

there is a massive atherosclerotic process extending continuously from the aortic ring to the lower abdominal region. That there was a difference in the ability of rabbits 29 and 32 to metabolize cholesterol there can be no question.

DEATH OF A RABBIT FROM CORONARY INSUFFICIENCY?

In figure 22 is reproduced a section of the aorta and the left coronary artery at its origin from rabbit 32. The aorta shows little change at this point. The contrast between the thick aortic media and the thin coronary wall is striking. There is also indicated the sharp curve which the left coronary artery takes as it leaves the aortic wall in its descending

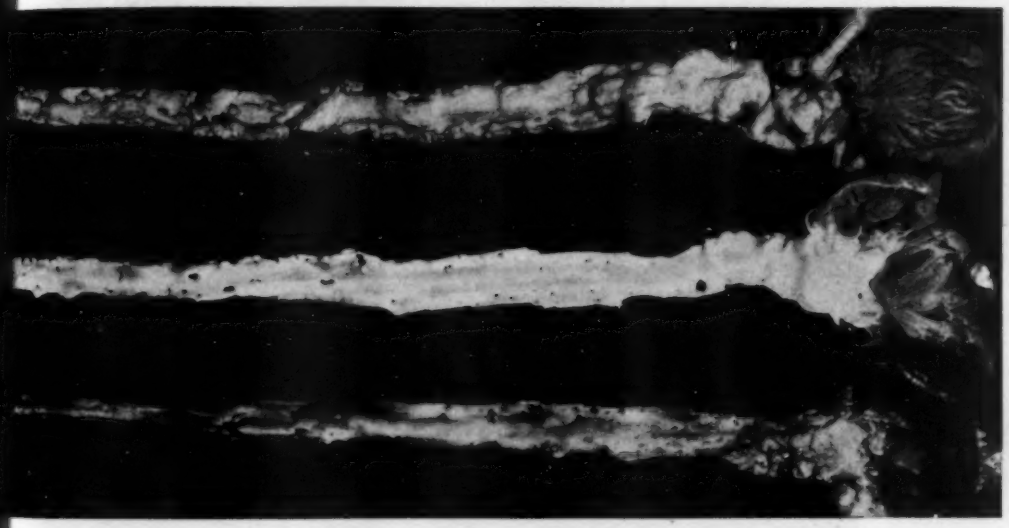

Fig. 21.—Hearts and aortae of rabbits. See text.

course. This curve is sharper than that taken by the human left coronary artery but is of similar character. The coronary lesion, still rich in lipoid cells, has narrowed the lumen of the vessel to a high degree. If a lesion of similar degree were discovered in the left coronary artery of a human being who was found dead with evidence of indigestion there is little doubt that the cause of death would be properly referred to coronary sclerosis and insufficiency.

CONCLUSIONS

From the comparative study of human and rabbit atherosclerosis the following conclusions are drawn: 1. The lesions of human atherosclerosis can be reproduced in the rabbit by the feeding of cholesterol. 2. The fibrosis which is characteristic of human coronary lesions in

the young is the characteristic lesion in cholesterol atherosclerosis in young rabbits. Fibrosis is therefore a reaction of youth and not of species. 3. The evolution of the lesions through lipoidosis, lipoid cell formation and fibrosis, more rapidly produced in experimental animals, can be followed in greater detail in these animals than in human lesions, in which progress is so slow that the stages in the progression are distinguished with difficulty.

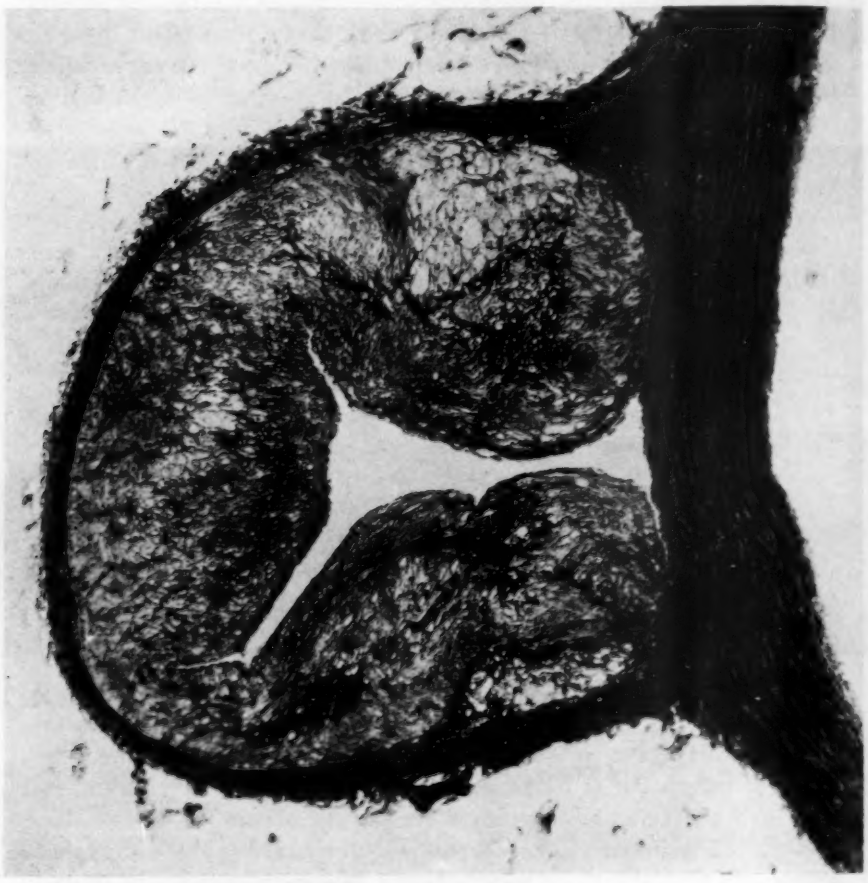

Fig. 22.—Aorta with left coronary artery of rabbit; × 65.

COMMENT

Any metabolic agent capable of producing atherosclerosis must have been an article of diet from early times, since atherosclerosis has been found in mummies.[11] One thinks of cholesterol in terms of blood or bile cholesterol. This, however, is only the mobilized cholesterol. The

11. Ruffer, M. A.: J. Path. & Bact. **15**:451, 1911.

substance is a necessary part of every animal cell, forming, from Starling's concept, the stable groundwork of the cell cytoplasm. As far as any one knows no cholesterol is synthesized by the human body. All of the supply is ingested. The most urgent demands for it come at times of most rapid cell formation. Egg yolk is intended for the embryo. Milk is intended for the infant. It is interesting to note that Wells, in his "Outline of History," records that it was relatively late in the evolution of primitive man that he developed what Wells calls "the rather unnatural use of animal's milk as food." The high blood cholesterol found in pregnant women marks the mobilization of this substance for the needs of the fetus in utero. Man is the only animal that ingests eggs and milk throughout its lifetime. Man is also the only animal, as far as is known, which dies in early life from coronary sclerosis, and which acquires atherosclerosis almost universally in advanced life.

That cholesterol, which is so highly insoluble, is modified during metabolism by union with other lipoids is probable from the work of Kimmelstiel.[12] Lipoid combinations which can be shown in vitro to increase the solubility of cholesterol were isolated by him from atherosclerotic aortae. It was only where atheromatous "abscess" formation had occurred, with the precipitation of cholesterol crystals, that a very high, almost exclusive cholesterol content was found. The absorption from the intestine and distribution of cholesterol in the body apparently depend on the combination of this substance with other lipoids. The failure to produce atherosclerosis in rabbits following intravenous injection of the pure substance may be due to this factor.

As one studies human atherosclerosis the analogy of the disease to diabetes repeatedly suggests itself. It is true that sugar is one of the most soluble and combustible food substances, and that its permanent storage in the body does not occur, while cholesterol is not combustible, its avenues of excretion are limited, and it tends to be stored. However, as in diabetes, marked variation in idiosyncrasy to the substance seems to exist. As in diabetes, the inheritance of a poor cholesterol metabolism appears to be associated with the tendency to an early death from coronary sclerosis. As in diabetes, advancing age, with the development of inefficiency of the cholesterol metabolism, appears to be associated with more frequent late manifestations of the disease. Finally, as in diabetes, an internal secretion, in this case that of the thyroid gland, appears to control the experimental production of atherosclerosis.

Recent human experience in diabetes supports the experimental findings in rabbits following cholesterol feeding. During and following

12. Kimmelstiel, P.: Virchows Arch. f. path. Anat. **282**:402, 1931.

the period when diets excessively rich in fat were used in the treatment of diabetes there was so great an increase of atherosclerosis that Shields Warren wondered whether the increase was due to the diabetes or to the treatment of the disease. Roentgen examination of the legs of some of the children treated disclosed evidence of calcified atherosclerotic arteries, and xanthomas were common. Recent reports from the Joslin clinic indicate that under a diet of lower fat content in the treatment of diabetes xanthomas no longer appear and roentgen evidence of calcified arteries in the legs of the children is lacking.

ABSCESSES OF THE LIVER CAUSED BY BACTEROIDES FUNDULIFORMIS

REPORT OF TWO CASES

DONALD C. BEAVER, M.D.

JOHN C. HENTHORNE, M.D.
Fellow in Pathology, the Mayo Foundation

AND

JOHN W. MACY, M.D.
Fellow in Medicine, the Mayo Foundation

ROCHESTER, MINN.

Under the generic designation Bacteroides Castellani and Chalmers,[1] in 1919, brought together a rather large group of anaerobic, nonsporulating bacilli which previously had been without systematic classification. The generic name Bacteroides proposed by these investigators was adopted by a committee of the Society of American Bacteriologists and given a place in their systematic classification, as recorded in "Bergey's Manual of Determinative Bacteriology."[2] According to the manual, the characters of the genus are: "Motile and nonmotile rods, without endospores. Show good growth on ordinary culture media; without pigment formation. Obligate anaerobes." Seventeen species are listed; ten are gram-positive, and seven, gram-negative. The species enumerated are described as normal inhabitants of the intestinal tract of man and as the cause of suppurative and gangrenous infection in man.

Veillon and Zuber,[3] in 1898, were apparently the first to describe anaerobic organisms of this type and to point out their importance. They obtained several species from cases of appendicitis and other suppurative conditions, to which they gave the name Bacillus ramosus, Bacillus serpens, Bacillus fragilis, Bacillus furcosus and Bacillus fusiformis. Hallé,[4] at about the same time, confirmed this work by finding similar organisms in the vaginal flora and in suppurative conditions about the genital tract of the female. He introduced a new species,

---

From the Department of Pathologic Anatomy, the Mayo Clinic.

1. Castellani, Aldo, and Chalmers, A. J.: Manual of Tropical Medicine, ed. 3, London, Baillière, Tindall & Cox, 1919.

2. Bergey, D. H., and others: Bergey's Manual of Determinative Bacteriology, Baltimore, Williams & Wilkins Company, 1925.

3. Veillon, A., and Zuber: Arch. de méd. expér. et d'anat. path. **10**:517, 1898.

4. Hallé, J., quoted by Teissier, Reilly, Rivalier and Stefanesco: Ann. de méd. **30**:97, 1931.

which because of its extreme pleomorphism was called Bacillus funduliformis. Rist [5] and Guillemot, Hallé and Rist [6] isolated forms similar to those described by Veillon and Zuber and by Hallé from pulmonary abscesses, empyema and infected ears. Cottet [7] described these organisms as the cause of phlegmonous periurethral infections; Gilbert and Lippmann,[8] as one of the causes of cholecystitis, and Gohn and Sachs,[9] as an etiologic factor in peritonitis. The work of these pioneer investigators has been confirmed by many others, a review of whose studies appears in the article by Teissier, Reilly, Rivalier and Stefanesco.[10] Of equal importance are the observations of Tissier,[11] Distaso,[12] Debono [13] and Eggerth and Gagnon [14] that organisms of this group are found frequently, and even predominate, in the flora of the normal intestinal tract of man.

In 1931 [15] and 1932,[16] Thompson and one of us (Beaver) reported two fatal cases of bacteremia due to gram-negative species of Bacteroides. The organism was identified in one case as Bacteroides fragilis, and in the other, as Bacteroides funduliformis. Infection was apparently primary in the genito-urinary tract of the male patient, with pulmonary abscesses secondary to the bacteremia. Although only two cases were reported, it was stated that similar organisms had previously been encountered in blood cultures in several cases, but that at the time of their appearance their significance was not recognized. Among these cases were two instances of carcinoma of the colon. A review of the literature during the period of these investigations revealed reports of ten instances of bacteremia due to gram-negative species of Bacteroides. In addition, a gram-positive species, Bacteroides ramosus, had been recovered in blood cultures.

Nonsporulating anaerobic bacilli of the genus Bacteroides in rare instances have been reported as the etiologic agents in hepatic abscesses.

---

5. Rist, Edouard: Centralbl. f. Bakt. **30**:287, 1901.

6. Guillemot, Louis; Hallé, Jean, and Rist, Edouard: Arch. de méd. expér. et d'anat. path. **16**:571 and 677, 1904.

7. Cottet, J., quoted by Teissier, Reilly, Rivalier and Stefanesco: Ann. de méd. **30**:97, 1931.

8. Gilbert, A., and Lippmann, A.: Compt. rend. Soc. de biol. **54**:1189, 1902.

9. Gohn, Anton, and Sachs, Milan: Centralbl. f. Bakt. **38**:131, 1906.

10. Teissier, P.; Reilly, J.; Rivalier, E., and Stefanesco, V.: Ann. de méd. **30**:97, 1931.

11. Tissier, H.: Ann. de méd. et chir. inf. **4**:675, 1900.

12. Distaso, Arcangelo: Centralbl. f. Bakt. **59**:97, 1911.

13. Debono, P.: Centralbl. f. Bakt. **62**:229, 1912.

14. Eggerth, A. H., and Gagnon, B. H.: J. Bact. **25**:389, 1933.

15. Thompson, Luther, and Beaver, D. C.: Proc. Staff Meet., Mayo Clin. **6**:372, 1931.

16. Thompson, Luther, and Beaver, D. C.: M. Clin. North America **15**:1611, 1932.

Norris,[17] in 1901, described a fatal illness due to multiple abscesses of the liver. There was an associated pylephlebitis, which suggests that the infection arose from within the distribution of the portal circulation. Two etiologic agents were described in this case: first, an anaerobic streptococcus similar to Micrococcus fetidus of Veillon, and second, an anaerobic bacillus similar to those which Veillon and Zuber had described as the causal factors in other suppurative processes. Harris,[18] in 1905, recorded a fatal illness characterized by multiple abscesses of the liver, lungs and spleen. The etiologic agent in this case was likewise recognized as similar to the anaerobic bacilli which had been described by Veillon and Zuber. Harris named the organism Bacillus mortiferus. Teissier, Reilly, Rivalier and Stefanesco, in 1931, reported four cases of bacteremia due to Bacteroides funduliformis. In one case the principal localization of the infection, probably the source of the bacteremia, was in the liver, where at necropsy multiple abscesses were found.

In a previous publication on hepatic abscesses by one of us (Dr. Beaver[19]) it was stated that staphylococci and streptococci were the usual etiologic factors. To these and other organisms enumerated should be added, apparently in a conspicuous position, members of the genus Bacteroides.

CLINICOPATHOLOGIC STUDY

We recently had the opportunity of studying two cases of abscesses of the liver in which Bacteroides funduliformis was identified as the etiologic agent. It seemed desirable to us that these cases be placed on record, since abscesses of the liver due to Bacteroides funduliformis have rarely been reported, and since they are expressions of infection with Bacteroides which are distinctly different from those previously reported from this institution.

In case 1, the primary lesion consisted of an infected, ulcerating carcinoma of the rectum, with metastasis to the regional lymph nodes, liver, lungs and left suprarenal gland. In the region of the rectal carcinoma, some veins were invaded by the growth and others were thrombosed. In some instances the thrombi were infected. Portal thrombosis and abscesses of the liver, closely associated with the metastatic carcinomas, were the terminal complicating factors. For obvious reasons it may be assumed that the hepatic abscesses and the hepatic metastatic growths of carcinoma arose through the same channel of dissemination, namely, from the rectum through the portal circulation.

17. Norris, Charles: J. M. Research **6**:97, 1901.
18. Harris, N. M.: J. Exper. Med. **6**:519, 1905.
19. Beaver, D. C.: Am. J. Path. **7**:259, 1931.

In case 2, no primary localization of the infection could be found at necropsy. The hepatic abscesses, however, had the general characteristics of abscesses disseminated by way of the portal circulation. They were large, somewhat multilocular and confined within the right lobe of the liver. It is probable, although not proved, that the hepatic abscesses in this case arose from a cryptic focus somewhere in the colon, appendix or rectum.

REPORT OF CASES

CASE 1.—A man, aged 64, for three months had had symptoms which were characteristic of rectal carcinoma. Proctoscopic examination and biopsy confirmed the diagnosis. A permanent left inguinal colonic stoma was made. Convalescence was uneventful until the seventeenth postoperative day, when there was a sharp rise in temperature to 102 F., with a pulse rate of 120 beats per minute. The fever continued as an irregular type, with morning remissions to a temperature of about 99 F. and afternoon rises to 100.2 or 102 F., and there were occasional chills. The patient became jaundiced; the bilirubin content was from 7.9 to 11.5 mg. per hundred cubic centimeters of serum, and the van den Bergh reaction was direct. The number of leukocytes ranged from 19,600 to 25,900 per cubic millimeter of blood The course was characterized by persistent, irregular fever and gradual decline, and the patient died three weeks after the fever began.

At necropsy the recent right rectus incision made for colostomy was well healed and in good condition. The peritoneal cavity contained 2,000 cc. of clear, light yellow fluid. The rectum revealed a large, annular polypoid, ulcerated and infected carcinoma. Metastasis had occurred to the regional fascia and lymph nodes and also to the aortic lymph nodes and the liver, lungs and left suprarenal gland. The liver weighed 3,670 Gm. It was greenish brown. The surface was nodular, the nodules having an appearance typical of metastatic carcinoma. The central portions of the nodules were usually firm and umbilicated, but in some nodules these areas were elevated and soft. Nodules were abundantly present throughout all parts of the liver. Those with softened central parts were revealed as metastatic carcinomas with central suppuration. The pus had a mildly disagreeable, rancid odor and was yellow. The extrahepatic and intrahepatic portions of the portal vein were thrombosed. In neither the wall of the vein nor the thrombus was there evidence of suppurative inflammation. Other organs were essentially normal.

Microscopically, the rectal neoplasm was a malignant epithelial cell growth, composed of newly formed, atypical glandular acini in polypoid formation. The surface of the growth was ulcerated and covered by a pseudomembrane, consisting of polymorphonuclear leukocytes, serum, fibrin and necrotic cellular detritus. The growth had extended into the muscularis, the surrounding fatty areolar tissue and some of the veins. In other veins there were thrombi in which were seen areas of necrosis with dense collections of polymorphonuclear leukocytes. The liver exhibited rather intense sinusoid congestion, frequently with central atrophy and necrosis. Sections of the nodular portions disclosed a malignant epithelial neoplasm, similar in appearance to the rectal carcinoma. The walls of the abscesses were composed of an outer zone of metastatic carcinoma and an inner zone of fibrous connective and granulation tissue; the more peripherally situated tissue consisted of rather dense, mature fibrils, whereas the inner portion was composed mostly of fibroblasts and young blood vessels. Throughout the walls were present

also polymorphonuclear neutrophilic leukocytes, lymphocytes and large mononuclear phagocytic cells. Within, the neutrophilic leukocytes gradually became predominant until the central zone of suppuration was approached. Here only polymorphonuclear neutrophils, fibrin, coagulated serum and necrotic detritus were found. More centrally the exudate was almost entirely necrotic. The abscesses were formed either entirely within a metastatic tumor nodule or at its side. Sections of the portal vein revealed a recently formed, bland thrombus, the peripheral portions of which were being organized. Metastatic carcinomatous nodules having a structure similar to that of the nodules in the rectum and liver were also found in the lymph nodes, lungs and left suprarenal gland. None of these nodules was infected.

CASE 2.—A man, aged 50, about Jan. 27, 1933, contracted what he thought was influenza. On February 9, he was seen by physicians of the Mayo Clinic. He complained of having vague pains in the right lower part of the thorax anteriorly and in the right upper quadrant of the abdomen, with cough, fever and weakness. On February 7, he had had a chill. Physical examination revealed him to be well developed, poorly nourished and dehydrated. He was breathing rapidly and was somewhat dyspneic. Examination of the thorax disclosed no definite limitation of movement on either side and no definite impairment of resonance, but the breath sounds seemed to be suppressed over the bases of both lungs, and a few crackling râles were heard over the base of the right lung. The abdomen was held rigid, and some tenderness was elicited on palpation below the right costal margin. The liver was not palpable. The temperature was 102 F.; the pulse rate, 96 beats per minute, and the blood pressure, 130 mm. of mercury systolic and 100 mm. diastolic. Roentgenologic examination of the thorax revealed bilateral elevation of the diaphragm and infiltration of the right cardiophrenic angle. The concentration of hemoglobin was 13.3 Gm. per hundred cubic centimeters of blood, and the leukocytes numbered 14,300 per cubic millimeter of blood, 90 per cent being polymorphonuclear neutrophils, 6 per cent, lymphocytes, and 4 per cent, monocytes. The fever became distinctly septic and was associated with severe chills and sweats. There were extreme variations between morning and afternoon temperatures, as recorded in figure 1. Leukocytosis persisted, the white cell count varying between 13,900 and 55,300 per cubic millimeter of blood; usually the count was more than 25,000, with about 90 per cent polymorphonuclear neutrophils in the differential smear. In two blood cultures there was no growth of micro-organisms. Mild icterus developed a few days before death. The course was characterized by progressive weakness, with gradual decline, and death occurred on March 7, 1933, forty days after the illness began.

At necropsy, several small, sharply demarcated nodular regions were found in the lower lobes of both lungs; these had a grayish-white, caseous center and a hemorrhagic periphery. The central portion of some of these had undergone suppuration, forming abscesses from 1 to 1.5 cm. in diameter. The liver weighed 3,190 Gm. The capsular surface was brownish red and generally smooth and glistening. Some portions rose above the general contour of the surface as nodular areas of irregular size which fluctuated on palpation. Throughout the right lobe there were multiple multilocular and unilocular abscesses. The pus had a mildly putrid, somewhat acrid odor and was thick and greenish yellow. In the periphery of the abscesses it was often more caseous than purulent. The abscesses varied in diameter from 0.5 to 10 cm., the smaller ones being arranged in clusters about the walls of a larger one, thus giving the area around the large abscess a multilocular appearance whereas the central abscess itself was almost entirely unilocular. There were no other significant pathologic changes.

Microscopically, in the lower lobes of the lungs there were small focal zones of bronchopneumonia. In other parts there were small abscesses from the central portions of which alveolar structures had disappeared and had been replaced by dense collections of polymorphonuclear neutrophilic leukocytes and also by zones of necrosis. In the exudate from the peripheral zone especially there were masses of bacteria which stained faintly with hematoxylin. In some sections there were only focal areas of hemorrhage. In the hepatic abscesses the exudate was composed centrally of granular, faintly eosin-stained, almost acellular material, but nearer the periphery it appeared as definite collections of fairly well preserved polymorphonuclear neutrophilic leukocytes, though areas of necrosis were still present. In this zone there were also many masses which stained faintly with hematoxylin—apparently colonies of micro-organisms. A few fibroblasts, newly formed capillaries, lymphocytes and large mononuclear phagocytes were also associated with this zone. In the abscess wall proper, connective tissue gradually became more dense, being at first predominatingly fibroblastic with a few newly

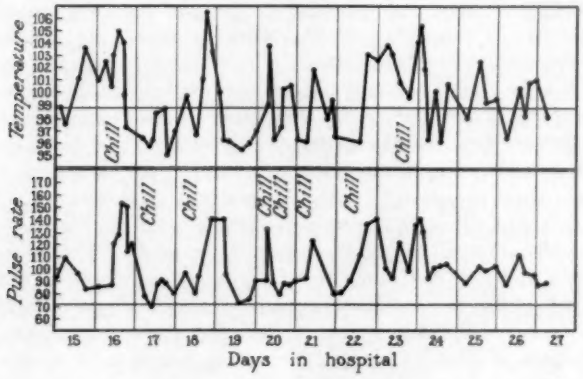

Fig. 1 (case 2).—A typical portion of the record of the temperature and the pulse rate from the twenty-eighth to the fortieth day of illness. Death occurred on the twenty-seventh day after admission and the fortieth day after the illness began.

formed capillaries and being transformed gradually into a peripheral encircling zone composed of mature fibrous connective tissue. Intermingled with the fixed tissue of the abscess wall there were a few polymorphonuclear neutrophilic leukocytes and a greater number of lymphocytes and large mononuclear phagocytes.

CLINICAL STUDY

On the basis of a review of cases reported in the literature and of personal experience, infections due to Bacteroides funduliformis and other species impress us as being worthy of serious consideration. This is true not only because infections of this type seem not to be rare but because they are serious and apparently often, if not usually, fatal.

So far as clinical manifestations of the pathogenicity of Bacteroides are concerned, there are no definite differential diagnostic points which

set this type of infection off from other severe pyogenic reactions. Blood cultures frequently become positive during the course of illness, but not always early; they should therefore be repeated if bacteremia is suspected. When positive, they serve as a means of identifying the type of infection. The symptoms and physical signs which are evoked naturally depend primarily on the points of localization. If there are distinctive features, however, they may be found in extreme toxic manifestations, as expressed by a high, septic type of fever, associated with chills, perspiration and a profound state of weakness progressing to exhaustion. These signs may be extreme and disproportionate to the actual physical expression of infection. The primary as well as the secondary points of localization may remain more or less obscure.

With the occurrence of infection of the liver, there were the usual clinical evidences of hepatic suppuration, which were expressed not only by the regional physical findings but by the high, irregular type of fever, with marked morning remissions and high afternoon exacerbations. There were associated chills and perspiration, with systemic evidence of severe toxicity and terminal jaundice. There was also marked leukocytosis, with polymorphonuclears predominating.

The pulmonary complications which accompanied one of the cases reported here were similar to those which Thompson and Beaver previously described. They consisted of septic infarction, bronchopneumonia and abscesses. Guillemot, Hallé and Rist and recently Cohen [20] have emphasized the pulmonic manifestations of infection with Bacteroides, particularly stressing putrid or gangrenous pulmonary abscesses and empyema. Pulmonary lesions may be only terminal embolic phenomena, appearing after an already established infection has provoked severe reaction. The emboli may invade the lung from primary and secondary situations elsewhere, as they did in case 2, or they may occur early in the course of illness, representing the secondary embolic localization of the infection from a primary situation elsewhere, as they did in the cases described by Thompson and Beaver. In the experience of others, pulmonary infections may be primary, apparently the result of aspiration, and may lead to putrid and gangrenous pneumonia, abscesses and empyema.

PATHOLOGIC STUDY

In our studies the primary lesions in infections with Bacteroides were found either in the genito-urinary tract, as previously reported by Thompson and Beaver, or in the colon, as in the cases reported here. They have been described by others as occurring in other portions of the body, as enumerated at the beginning of this paper. The colonic lesion may occur at the site of ulcerating carcinoma, as in case 1, or from

20. Cohen, John: Arch. Surg. **24**:171, 1932.

some unrecognized focus, as in case 2. In the latter instance the assumption that a lesion existed in the colon is only presumptive, although there is some support for this conclusion. If the primary lesion is colonic, it is within the distribution of the portal circulation, and secondary manifestations of embolic hematogenous dissemination will be found in the liver, as they were in the cases reported here. If the primary lesion is low in the rectum, the direct dissemination of the infection may be through the caval circulation, with secondary embolic manifestations in the lungs. This was apparently also the route of dissemination of the infection from primary localizations in the prostate gland and urinary bladder, as previously referred to in the cases reported by Thompson and Beaver. If secondary infection results in the liver, the lungs and other tissues eventually may become involved as the bacteremia becomes established in the pulmonary and general circulation, as in our case 2; likewise, if the secondary localization is pulmonic, other organs may become involved as the bacteremia invades the general circulation. In the cases reported by other investigators the infection has sometimes had a more widespread dissemination than we have seen, involving the lungs, pleura, liver, kidneys and skin.

Bacteroides funduliformis and other pathogenic species are probably normal inhabitants of the oral and pharyngeal cavities, and most assuredly of the intestinal tract, as similar species have been found there by other investigators. Just how and why these organisms become pathogenic is unknown, but it may be assumed that while in their natural saprophytic existence they ordinarily cannot evoke inflammatory reactions, as soon as local injury occurs or they become transported to tissues elsewhere which by nature do not favor the saprophytic existence of bacteria they become distinctly parasitic and provoke a profound toxic reaction. Teissier and his co-workers felt that the primary localization of this type of infection may be pharyngeal. This might account for the frequency with which the organisms have been found in pulmonary abscesses and empyema. Infection of the intestinal tract and structures in close anatomic relationship seems to make it evident that the primary focus may be in these structures. This opinion is supported by the finding of organisms of this genus as one of the dominant types of organisms in the intestinal flora. It receives further support from the occurrence of infection of certain portions of the intestinal tract and of the male and the female genital tract and from the finding of abscesses of the liver caused by Bacteroides coexistent with metastatic colonic carcinoma, as in our case 1.

The pathologic anatomy of infection with Bacteroides as revealed in the liver and lungs in our cases was somewhat distinctive. The abscesses in the liver were large, with a tendency to be multilocular, especially in

the peripheral portion (fig. 2 *A*). The exudate was thick, tenacious and usually distinctly purulent, although in smaller lesions it tended to be caseous. The exudate was from white to light yellow or greenish yellow, and it emitted a peculiar, mildly putrid or acrid odor sometimes resembling the odor of butyric acid. The abscesses were usually well encapsulated by fibrous connective tissue, in which newly developed vascular channels formed a prominent part. Most of them were chronic (fig. 2 *B*). In the exudate, polymorphonuclear neutrophilic leukocytes

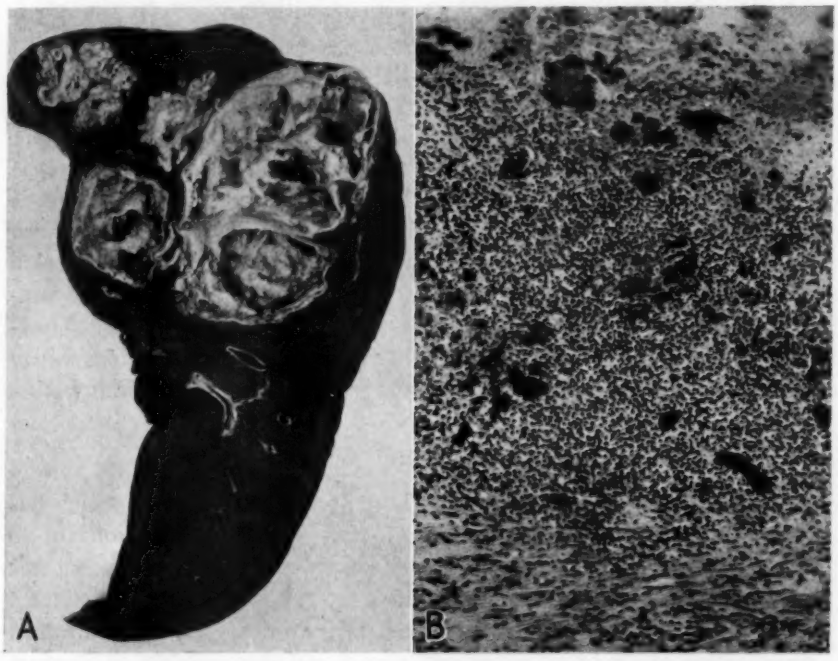

Fig. 2 (case 2).—*A* shows large multilocular and unilocular abscesses in the right lobe of the liver. *B*, a microscopic view of an abscess. Numerous colonies of micro-organisms are prominent (hematoxylin and eosin; × 100).

predominated. The fixed tissues in the region of the infection, as well as the exudate itself, were partially necrotic. In the lungs the lesions had the appearance of small, septic or bland infarcts, abscesses or patches of bronchopneumonia. Usually the lesions were solid, firm and grayish or of a hemorrhagic color. The grayish nodules appeared as solid regions of necrosis, somewhat caseous. All transitional forms existed to small abscesses with definite suppuration. Large, putrid or gangrenous abscesses in the lungs, with putrid empyema, such as have been reported by others, were not observed. Such lesions as these are apparently primary in the lung and usually the result of aspiration.

Primary lesions of the genito-urinary tract and colon, as we have observed them, are less distinctive, since the bacterial flora in these situations has always been mixed.

Abscesses of the liver caused by Bacteroides funduliformis must be distinguished from amebic abscesses, actinomycotic abscesses and abscesses due to other pyogenic micro-organisms, such as staphylococci and streptococci. Grossly, they all bear a superficial resemblance to one another, although there are certain features which may serve to distinguish them. Amebic abscesses are usually solitary and unilocular and associated with amebic colitis, although the lesions in the colon may be healed. Actinomycotic abscesses, as a rule, have heavy fibrous and granulomatous tissue capsules, frequently with associated sinus tracts. Abscesses of the staphylococcic or the streptococcic type more often are associated with suppurative pylephlebitis and have a more distinct multilocular or honeycomb appearance, similar to that of the abscesses caused by Actinomyces. The final differential diagnosis is dependent on microscopic and bacteriologic examinations. Of course, amebic colitis may be preceded or followed by infection of the colon with pathogenic bacteria or vice versa. This possibility must be considered in connection with organisms of the genus Bacteroides. However, in the cases of abscesses of the liver caused by Bacteroides which we have studied, no evidence of primary or secondary amebic infection has been found.

BACTERIOLOGIC STUDY

The bacteriology of Bacteroides is the particular obstacle which has led to the relative lack of recognition of this type of infection for so long. The organisms are obligate anaerobes, and the pathogenic varieties at least develop on culture mediums with much difficulty except when the medium is enriched by blood, serum or tissues. When mixed infection exists, their isolation may prove still more trying. However, when they are obtained in blood cultures, the culture is usually pure. Their biologic reactions are extremely difficult to observe because they do not grow readily on differential mediums. They are extremely pleomorphic, often being filamentous.

The cultural characteristics of Bacteroides funduliformis recently (1931) were well studied by Teissier, Reilly, Rivalier and Stefanesco with organisms isolated from four cases of this infection. The organisms in our cases agree in all essentials of morphologic structure and biologic reactions with those described by the investigators named. Since in our cases the two strains were practically identical morphologically and culturally, they will be described together, exceptions being noted whenever necessary. In case 1 the organism was isolated from the hepatic abscess only, but in case 2 the cultures were obtained from both the hepatic abscess and the blood of the heart.

Microscopic sections of fixed tissue from the hepatic abscesses were stained by Brown's modification of Gram's stain. In case 1, the organisms appeared in small clusters or tufts in the peripheral portion of the exudate. They were irregularly placed in a sort of criss-cross arrangement. The individual organisms appeared as plump, straight, long, unbranched rods and filaments with rounded ends. They were gram-negative (fig. 3 *A*). In case 2, the organisms were relatively short,

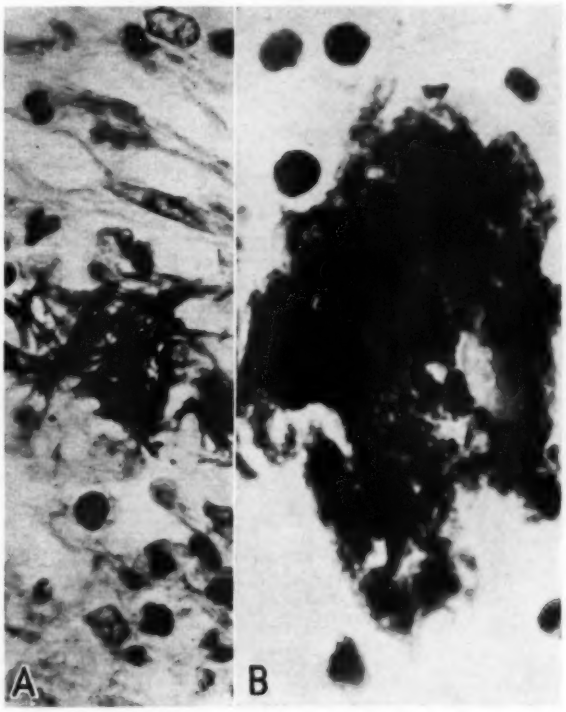

Fig. 3.—*A* shows a colony of micro-organisms in a section of tissue from the hepatic abscess in case 1 (Brown-Gram stain; × 1,700). *B* shows a colony of micro-organisms in a section of tissue from the hepatic abscess in case 2 (Brown-Gram stain; × 900).

plump, gram-negative bacilli with rounded ends, frequently with bipolar granules, and were usually closely massed in clusters, making the identification of individual forms extremely difficult (fig. 3 *B*). In this case similar masses of organisms were found also in the pulmonary abscesses.

On culture mediums marked morphologic variations were observed, apparently dependent on the age of the culture, the type of medium employed or other unknown factors of growth. In a general way, the

more extreme variations in involution were found in cultures on solid mediums, such as hormone blood agar, hormone serum agar and Löffler's serum, although varying degrees of dissociation were observed in cultures in liquid mediums, especially in certain of the dextrose broth solutions. In dextrose-brain broth the usual form was a short, plump rod with rounded ends, or a slender, slightly longer, rod, likewise with rounded ends. Occasionally filaments were seen. The rods frequently had deeply stained granules or bars distributed throughout the

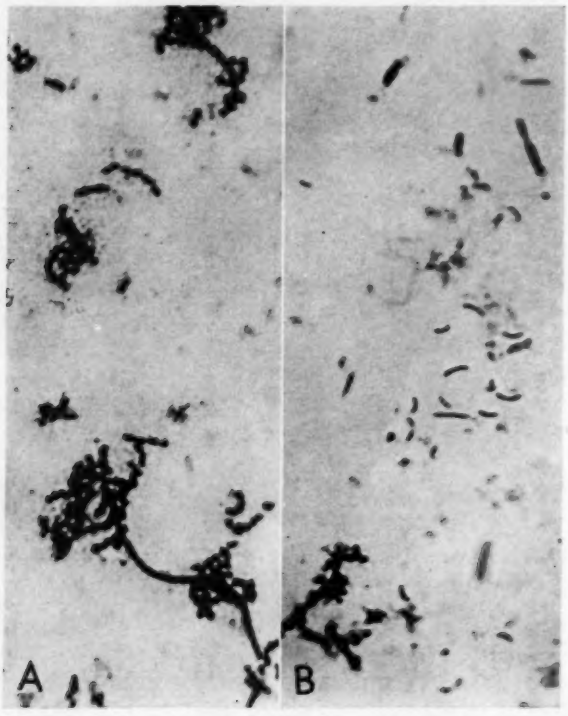

Fig. 4.—*A* shows coccobacillary and filamentous forms in a forty-eight hour brain broth culture (carbolfuchsin stain; × 1,500). *B* shows comma-shaped forms in a twenty-four hour brain broth culture from the peritoneum of rabbit 1 (carbolfuchsin stain; × 1,250).

cell, only polar granules being present in the shorter forms. The latter appeared as coccobacillary forms, which when in chains closely resembled chains of streptococci (fig. 4 *A*). Occasionally the rods were evenly stained, and in these, especially when filamentous, dissociation into granular or streptococcic types could be observed in all gradations from uniformly staining cells to chains of granules resembling streptococci. Slender, comma-shaped rods were further variants (fig. 4 *B*). Clumping of the organisms was usual. In older broth

cultures there was a gradual reduction in the number of stainable organisms; preparations of old but living cultures had the appearance of amorphous detritus. Young cultures on solid mediums were similar to young cultures on brain broth, but as the cultures on solid mediums increased in age, large numbers of swollen forms appeared (fig. 5 *A*). These were also seen to some degree in older broth cultures, but were less numerous. The swollen forms were often cigar-shaped, with bluntly rounded ends; the cell bodies were faintly stained, and deeply

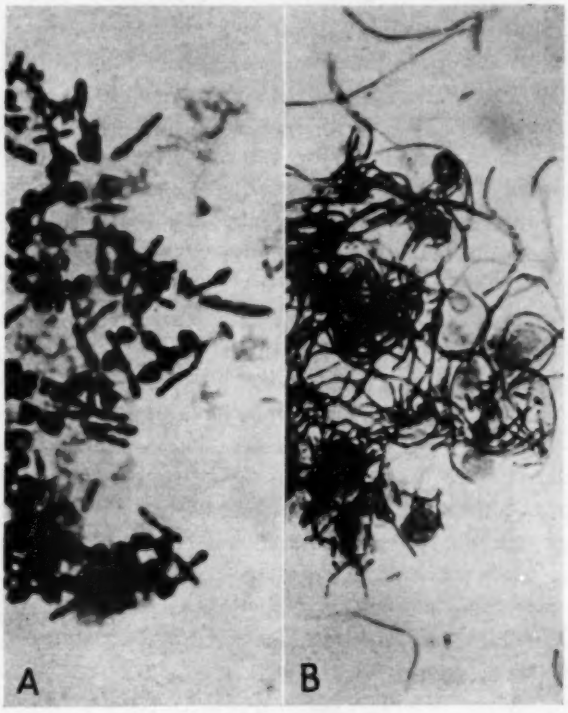

Fig. 5.—*A* shows swollen, typical types of Bacteroides funduliformis in a four day brain broth culture (carbolfuchsin stain; × 1,800). *B* shows filamentous forms in a five day blood agar culture (carbolfuchsin stain; × 825).

stained granules, beads or bars were present. The swollen forms were at other times oval or spherical. The oval or spherical forms were frequently deeply stained, without granules; some, however, were almost invisible, so faintly did they take the dye. On solid mediums, unbranched, uniformly stained filaments frequently predominated. These often were arranged in tufts (fig. 5 *B*). Less frequently the filaments were faintly stained, only the outer envelop becoming visible; this envelop surrounded an unstained, tubelike or hypha-like structure in which there were small stained granules or bars. These filaments

revealed, here and there, oval enlargements, which appeared to be the result of longitudinal splitting and swelling of the filaments, rather than spores, which they resembled. On further study such forms always reverted to the original coccobacillary type; otherwise one might assume that they represented contaminants.

The organisms were always gram-negative and never acid-fast. They were nonmotile. The usual aniline dyes, such as safranine and methylthionine chloride, U. S. P. (methylene blue), stained them faintly. They were well stained by dilute carbolfuchsin.

Cultures in dextrose-brain broth were allowed to stand at room temperature. After seven months (case 1) and four and a half months (case 2) they were still viable. They were readily susceptible to heat; a temperature of 56 C. was sufficient to kill cultures on dextrose-brain broth in two and five minutes (cases 1 and 2 respectively).

Dextrose-brain broth was found to be the most satisfactory medium for routine culturing of the organisms. Under the conditions present in this medium no precautions were necessary for obtaining growth anaerobically. Visible growth appeared in from one to seven days at 37.5 C. The rapidity of the appearance of growth apparently depended on the degree of anaerobiosis and on the number of organisms present in the inoculum. Evidence that growth was present became manifest at first by the formation of bubbles of gas in the region of the particles of brain at the bottom of the tube. As the bubbles enlarged they tended to rise to the surface of the tube. Rarely was gas formed so rapidly that bubbles accumulated on the surface of the medium. Next to the formation of gas, the medium gradually became turbid in the region of the particles of brain, this progressing to form eventually a layer of fine flocculi overlying the brain. Usually, unless disturbed, the medium remained clear, but occasionally it became slightly cloudy. The cultures had a mild, stale, putrid odor which gradually took on the odor of butyric acid. The brain was not blackened or digested. Tests of the gas rising from the tubes were negative for hydrogen sulphide.

No growth appeared on hormone agar, hormone blood agar, hormone serum agar or plain broth when allowed to incubate aerobically at 37.5 C. for several days. Satisfactory conditions for growth were obtained in these and other mediums by the use of pyrogallol and sodium hydroxide to absorb the oxygen. Anaerobic plating was successful in Spray plates. Slanted solidified mediums—gelatin, broth, milk, sugar fermentation tubes and similar preparations—were inoculated and placed in a Novy type anaerobic jar, with pyrogallol and sodium hydroxide added as before mentioned.

On hormone blood agar Spray plates, after twenty-four hours' incubation at 37.5 C., very small, scarcely visible, pinpoint-like colonies

appeared. A small zone of partial hemolysis surrounded each colony on examination with a hand lens. After forty-eight hours' incubation, surface colonies were discrete, slightly translucent, round, flat or slightly convex, moist, bluish gray and 1 mm. or less in diameter. A hemolytic zone surrounding each colony became distinct. Deep colonies were grayish white, opaque, round or lens-shaped and 0.5 mm. or less in diameter. A clear zone of hemolysis, from 1 to 3 mm. in diameter, surrounded each deep colony. At this time the growth resembled in appearance that of hemolytic streptococci. As plates were observed over a period of days, surface colonies became flat and rather dry and frequently had a deep opaque center, with a surrounding halo-like ring of growth. Deep, lens-shaped colonies and others became irregular, often with formations resembling Maltese crosses.

On hormone human blood agar slants, after forty-eight hours there was abundant growth of small, discrete, rounded, moist, somewhat translucent and slightly convex, bluish-gray colonies along the line of inoculation. Hemolysis was present. The condensation water became cloudy. On hormone human serum agar slants, growth was similar but less abundant. On plain hormone agar slants, usually there was no visible growth after two weeks; an occasional colony similar to those on blood agar appeared. On plain agar slants there was no visible growth after two weeks. On plain gelatin, there was no visible growth or liquefaction after two weeks. On gelatin plus human blood serum, sparse, small, irregular-shaped colonies appeared; there was no liquefaction at the end of two weeks.

In plain broth there was no visible growth after two weeks. In plain broth with coagulated egg white added, the medium remained clear and there was a slight flocculent growth at the bottom of the tube. There was no digestion of egg at the end of two weeks. On Löffler's blood serum there were almost imperceptible fine, discrete, slightly elevated colonies. There was no liquefaction of the serum after two weeks. There was no change in litmus milk after two weeks.

Peptone fermentation medium, with various sugars added, was inoculated and incubated anaerobically at 37.5 C. Growth failed to appear. Similar tubes to which 0.5 cc. of fresh human serum was added revealed abundant growth. Acid and gas were formed in dextrose, levulose and maltose. There was neither acid nor gas in sucrose, mannitol, xylose, galactose or lactose. Other sugars were not tried.

EXPERIMENTAL STUDY

Tests for pathogenicity were made on four guinea-pigs and nine rabbits. Guinea-pigs 1 and 2 and rabbits 4, 5, 6 and 7 were inoculated with forty-eight hour dextrose-brain broth cultures of blood from

case 1. Rabbit 1 was inoculated intravenously with 0.5 cc. of a dilution in physiologic solution of sodium chloride of pus from an abscess of the liver in case 2. The remaining two guinea-pigs (3 and 4) and four rabbits (2, 3, 8 and 9) were inoculated with forty-eight hour dextrose-brain broth cultures of blood from case 2. Inoculations were carried out in guinea-pigs subcutaneously and intraperitoneally and in rabbits subcutaneously and intravenously. In general, the organisms

Results of Animal Inoculations

Animal	Dose* and Method of Administration	Time Between Injection and Death	Result	Organism Recovered From
Guinea-pig 1	2.5 cc. subcutaneously	14 days (killed)	Subcutaneous abscess; drained spontaneously	Abscess
Guinea-pig 2	2 cc. intraperitoneally	21 days (killed)	No pathologic change	
Guinea-pig 3	1.5 cc. subcutaneously	33 days (killed)	Some early induration; recovered	
Guinea-pig 4	2 cc. subcutaneously	16 days (killed)	Subcutaneous abscess; drained spontaneously	Abscess
Rabbit 1	0.5 cc. intravenously (pus from abscess of liver)	Less than 15 hours	Beginning peritonitis	Peritoneum
Rabbit 2	0.6 cc. intravenously	5 days	Death due to other causes	
Rabbit 3	2 cc. subcutaneously	11 days (killed)	Subcutaneous abscess	Abscess
Rabbit 4	0.6 cc. intravenously	3 days	No pathologic change	
Rabbit 5	2 cc. subcutaneously	11 days	Subcutaneous abscess; multiple small hepatic abscesses, up to 1 mm. in diameter	Subcutaneous abscess; liver
Rabbit 6	0.5 cc. intravenously	51 days (killed)	Moribund on fourth day; recovered	
Rabbit 7	1.5 cc. intravenously	8 days	No pathologic change	
Rabbit 8	1.5 cc. intravenously	9 days	Purulent pleurisy; two hepatic abscesses, 1 cm. in diameter	Blood; hepatic abscess
Rabbit 9	0.5 cc. intravenously	14 days	Purulent pleurisy	Blood; pleural pus

* All injections, except for rabbit 1, were of forty-eight hour brain broth cultures.

were found to be somewhat less virulent than Thompson and Beaver had previously reported. The reactions, however, were similar. The results are summarized in the table.

Macroscopically, all of the abscesses contained thick yellow pus, which emitted a mildly putrid odor. Microscopically, they were usually chronic, with well defined granulomatous reactions. They contained a central area of necrotic material in which only a few leukocytes were found. Polymorphonuclear neutrophils and large mononuclear leukocytes became predominant peripherally. Mononuclear forms and lymphocytes gradually increased in number in the wall of the abscess, where fibroblasts and newly formed blood vessels also were present. Rarely giant cells were observed in this granulomatous zone. Sur-

rounding each abscess, connective tissue finally became dense and fibrous. Some of the abscesses were multilocular. In the muscle bundles near the subcutaneous abscesses there were granular degeneration and fragmentation, and about the vessels there were perivascular collections of leukocytes and lymphocytes. Gram stains of sections demonstrated that the bacteria occurred in dense masses of short, plump, coccobacillary forms within the abscess cavity. In a section of the subcutaneous abscess of rabbit 3, the organisms appeared in clusters of filamentous forms, as they did in sections of a hepatic abscess in case 1. The organisms in all sections studied were gram-negative.

SUMMARY

Two cases of hepatic abscess caused by Bacteroides funduliformis have been presented. The genus Bacteroides (Bergey) comprises certain anaerobic, nonsporulating bacilli. Organisms of this type were first described by Veillon and Zuber and by Hallé as the etiologic agents in various suppurative and gangrenous infections of man. Similar species also have been isolated from the normal intestinal flora of man.

It is probable that infections of this type are not rare and that there are two regions which seem particularly vulnerable to primary infection, namely, the large bowel and the genito-urinary tract of the male. In the colon, infection appears to take origin principally in infected carcinomas, although the focus may be cryptic. From the primary focus, direct hematogenous dissemination may occur to the liver or the lungs, with clinically demonstrable bacteremia frequently supervening. Such infections are extremely serious and entail a grave prognosis. The clinical syndrome produced is an extreme degree of toxicity, with a high, remittent type of fever, chills, perspiration and weakness which progresses to exhaustion. The physical findings vary with the points of localization.

The lesions of the liver, as we have observed them, have been essentially chronic granulomatous abscesses, frequently multilocular and spreading with extreme destructive changes, necrosis of tissue and exudation. In the lungs, the lesions have appeared as small septic infarcts, patches of bronchopneumonia or small abscesses. Most commonly found were firm, solid, grayish or hemorrhagic nodules, the grayish areas resembling beginning caseation necrosis. Other investigators have described large putrid or gangrenous abscesses of the lungs with empyema associated with organisms of this group. Such lesions are apparently primarily pulmonic, usually on the basis of aspirated infection. Guinea-pigs and rabbits are susceptible to experimental inoculation with Bacteroides funduliformis. The lesions produced are abscesses, similar in appearance to those occurring in man.

ISOLATION OF ETHER FROM HUMAN TISSUES

ALEXANDER O. GETTLER, PH.D.
AND
HENRY SIEGEL, B.S.
NEW YORK

The problem of proving definitely the presence of ethyl ether, $(C_2H_5)_2O$, in human tissues has remained unsolved to the present time. There are no specific color or precipitation reactions for ether. Methods used by Nicloux,[1] Shaffer and Ronzoni,[2] Haggard[3] and Spenzer[4] for the quantitative determination of ether are based on oxidation-reduction reactions. These are not specific qualitative tests for ether. Many organic substances, such as hydrocarbons, alcohols, aldehydes, ketones and organic acids, react as ether does toward these oxidizing agents. In medicolegal cases the pathologist or toxicologist has to rely on his sense of smell. When the body cavities are opened, he seeks the odor of ether. Proof of this kind is unsatisfactory and often misleading. For example, odors of various kinds may be encountered in body cavities and in organs which at times may simulate that of ether and at other times may conceal the odor of ether when it is present. The problem we set out to solve was the actual isolation of ether in pure form from the organs and its identification by determination of the boiling point.

Gettler, Niederl and Benedetti-Pichler,[5] in their contribution on the isolation of ethyl alcohol from human tissues, devised a specially constructed rectification flask. This apparatus was used at first in the attempt to isolate ether from tissue distillates. It served the purpose quite well. We succeeded in isolating droplets of ether, proving the same by determinations of the boiling point.

It was found that certain structural changes in the rectification flask not only would facilitate the isolation of the ether, but would also allow

---

Contribution from the chemical laboratories of the Chief Medical Examiner's Office, Bellevue Hospital, and of Washington Square College, New York University.

1. Nicloux, M.: Compt. rend. Soc. de biol. **61**:606, 1907.
2. Shaffer, P. A., and Ronzoni, E.: J. Biol. Chem. **57**:741, 1923.
3. Haggard, H. W.: J. Biol. Chem. **56**:127, 1923.
4. Spenzer, J. G.: Arch. exper. Path. u. Pharmakol. **33**:407, 1893.
5. Gettler; Niederl and Benedetti-Pichler: Mikrochemie **11**:173, 1932; J. Am. Chem. Soc. **54**:1479, 1932.

the collection and measurement of practically all of the ether present in the tissues. The changes in the microrectification flask (fig. 1) are:

1. The bulb of the flask is of larger capacity (300 cc.). This enables one to use the entire original tissue distillate rather than small aliquot portions. In this way the volumes of ether isolated are large enough to be measured.

2. A glass tube running to the bottom of the flask is fused into the side of the flask. This facilitates the introduction of the material from

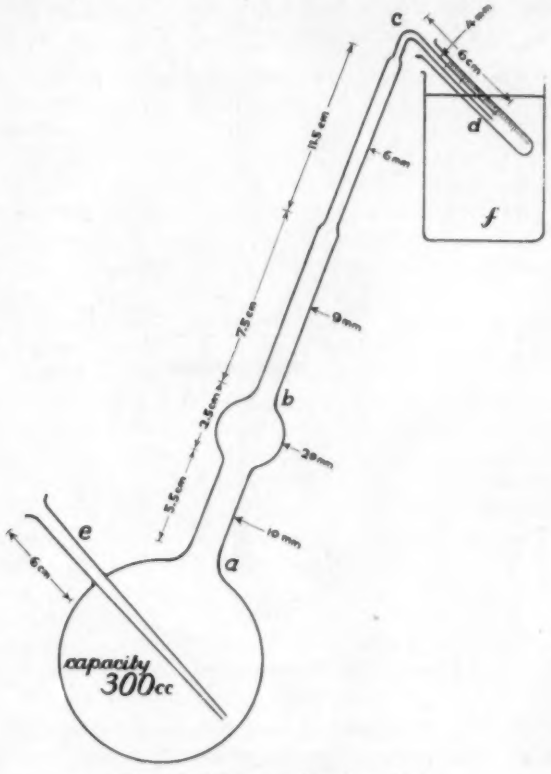

Fig. 1.—Microrectification flask.

which the ether is to be isolated, serves as a safety tube during the distillation and makes it easier to empty and clean the flask.

3. The uppermost S-shaped part is straightened out and points downward at an angle of 45 degrees to the main tube of the flask. This was done so that all the ether could be collected in one portion rather than in a series of successive drops.

METHOD OF ISOLATING ETHER FROM TISSUES

The tissues or organs removed at autopsy are placed quickly in glass jars, tightly sealed and put in a refrigerator. When ice cold, about 600 Gm. is quickly

ground up. The grinder is previously cooled by applying ice. Of this ground material, 500 Gm., is rapidly weighed out, mixed with 200 cc. of ice cold water and placed in a 2 liter flask. An additional 300 cc. of water and 1 cc. of liquid petrolatum are added. The mixture is distilled with steam, a long, well cooled condenser, the tip of which has been bent to resemble an adapter, being used. The bent tip should dip into 25 cc. of ice water contained in the receiving flask, the latter being at all times entirely surrounded by ice. Two hundred cubic centimeters of distillate is collected. This is ample for recovering all the ether that is present in the tissues. The distillate is now ready for the isolation of the ether.

The rectification flask already described is used. It must be clean, and part of it (from *b* to *d*) must be dried by playing a gentle flame over the outside surface.

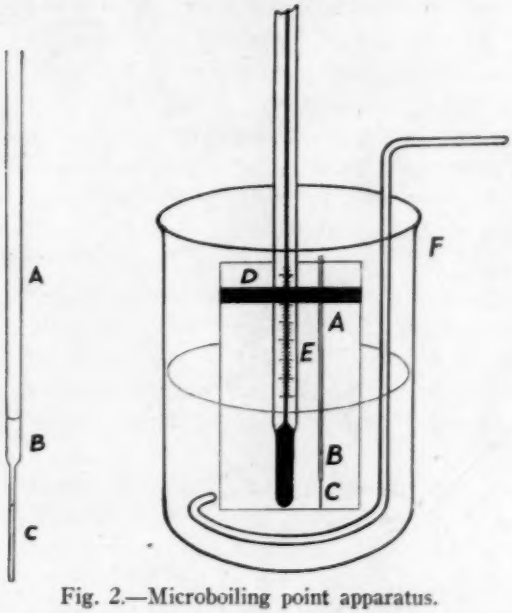

Fig. 2.—Microboiling point apparatus.

The entire 200 cc. of distillate is poured through the safety tube (*e*) into the rectification flask. One gram of granulated zinc is added. The receiving tube (*d*), which is 6 mm. in diameter on the inside and is graduated in twentieths of a cubic centimeter, is surrounded by a bath (*f*) of solid carbon dioxide in acetone, and should contain about 0.15 cc. of water (not more), so that the ether is collected over water as a separate layer. The rectification flask is now heated carefully and slowly, an asbestos centered wire gauze and a microburner being used. As soon as the solution begins to boil, the flame is regulated so that the liquid boils gently in the bulb for about fifteen minutes. During this time the steam (as indicated by a visible rise of the condensate or by running the hand along the tube and determining the height of the steam by the temperature) must not be permitted to rise beyond *b*. This is done by properly regulating the flame. The part of the tube from *a* to *c* acts as a reflux for the steam, while the ether vapors rise past *c*, condense and collect in the receiver. After mild boiling has been continued for fifteen minutes, the flame is gradually increased so that the steam is made to rise

slowly (in one minute) until it just passes the bend *c*. Rectification is now completed. The ether, if present, will be found unfrozen in the calibrated receiver. It sometimes happens that water vapor freezes in the tube beyond *c*, clogging it up; back pressure developed by continued heating will force the distillate out through the safety tube *e*. In that case, the flame is removed; then the receiving tube is removed, and the portion of the tube from *c* to *d* is warmed with the fingers. When the ice melts, it will be sucked back into the flask. The receiving tube is replaced and the rectification continued.

When the rectification is completed, as indicated by steam having passed the bend (*c*), the receiving tube is removed from the acetone bath, lightly stoppered and allowed to stand at room temperature until any ice in the calibrated receiving tube melts. The volume of recovered ether (upper layer) is read immediately.

In order to identify this upper layer as ether, the microboiling point is determined. We are convinced that the isolated ether need not be dried for determination of the boiling point. The isolated ether can be sealed in a capillary tube and kept as corpus delicti.

Determination of Boiling Point.[6]—A capillary tube (fig. 2 *A*), from 1.5 to 2 mm. in diameter, is drawn out into a finer capillary tube at one end (*C*), about 8 mm. in length. The end (*C*) of the capillary tube is introduced into the ether to be tested. By capillary action, ether is drawn into the tube. Care must be taken to allow only a small droplet to enter. The tube is then sealed by bringing the tip of it into the edge of a Bunsen flame for a second. As the walls of the tube are extremely thin, they fuse together almost instantly. Sealing in this way always leaves a bubble of air in the tip of the tube, between the sealed portion of glass and the drop of liquid (fig. 2 *C*). This bubble of gas serves to prevent superheating of the liquid during the determination of the boiling point. The capillary tube (*A*) containing the drop of liquid and a thermometer (*E*) are then mounted on a microscope slide and set up in a beaker (*F*) containing water, together with a stirrer. The temperature of the bath is raised slowly and uniformly. According to Emich, the true boiling point of a pure liquid is the temperature at which the droplet in the capillary reaches the surface of the bath. This is true only, however, if the bubble of gas in the tip of the tube is so small that the effect of its expansion is negligible, and also if the temperature of the bath is raised regularly and uniformly throughout.

A series of determinations were made on the boiling point of pure, dry ether as well as of ether that had been in contact with water for an indefinite period. The boiling points obtained were: pure, dry ether, from 34.8 to 35 C., and moist ether, from 34.7 to 35 C. Since the boiling point of moist ether is practically the same as that of dry ether, it is not necessary to dry a sample of ether before determining its boiling point.

RECOVERY OF ETHER FROM TISSUES

Five hundred gram portions of brain tissue and liver tissue were used. Varying amounts of accurately known quantities of ether were added to the tissues. All possible precautions were taken to avoid loss of ether due to vaporization. The method outlined was used to recover the ether which had been added to the tissues. The results are given in table 1.

6. Emich, F.: Monatsh. f. Chem. **38**:219, 1917.

TABLE 1.—*Study of Recovery of Ether*

Number	Tissue Used, 500 Gm.	Ether Added, Cc.	Ether Recovered, Cc.	Ether Lost, Cc.	Per Cent Recovery
1	Brain	0.06	0.03	0.03	50
2	Brain	0.06	0.03	0.03	50
3	Brain	0.12	0.05	0.07	42
4	Brain	0.12	0.07	0.05	60
5	Brain	0.15	0.10	0.05	67
6	Brain	0.15	0.09	0.06	60
7	Liver	0.30	0.24	0.06	80
8	Brain	0.30	0.25	0.05	83
9	Brain	0.45	0.37	0.08	82
10	Brain	0.45	0.38	0.07	84
11	Liver	0.60	0.47	0.13	78
12	Brain	0.72	0.63	0.09	88
13	Brain	0.75	0.67	0.08	89
14	Brain	0.90	0.78	0.12	87
15	Brain	0.90	0.74	0.16	82

TABLE 2.—*Analysis of Cases in Which Death Was Due to Ether*

Patient	Comment	Tissue Used, 500 Gm.	Ether Recovered,* Cc.	Boiling Point of Isolated Ether
M. R.	Died before fully anesthetized	Brain	0.03	....
		Liver	0.01	....
		Lung	None	....
J. P.	Died after a few inhalations of ether	Brain	0.09	34.8
		Liver	0.08	34.9
		Lung	0.02	....
E. W.	Died on table; no operation	Brain	0.19	28.5†
T. J.	Died on table; no operation	Brain	0.50	34.9
		Liver	0.30	34.9
		Lung	0.34	34.7
W. O.	Died on table just after operation	Brain	0.11	35.0
		Lung	0.10	35.0
		Liver	0.14	34.6
M. J.	Anesthesia stopped, 15 minutes	Brain	0.37	....
G. W.	Anesthesia stopped, 30 minutes	Brain	0.21	35.1
		Liver	0.22	34.9
		Lung	0.14	35.0
T. M.	Anesthesia stopped, 70 minutes	Liver	0.11	35.0
		Lung	0.09	34.5
W. W.	Anesthesia stopped, 75 minutes	Brain	0.09	....
J. L.	Anesthesia stopped, 85 minutes	Brain	None‡	....
R. F.	Anesthesia stopped, 4½ hours	Brain	None	....
L. A.	Anesthesia stopped, 7½ hours	Brain	None	....
L. J.	Anesthesia stopped, 16 hours	Brain	None	....
R. R.	Anesthesia stopped, 20 hours	Brain	None	....

* This is approximately 84 per cent of the amount of ether actually present in 500 Gm. of tissue.

† This ether contained ethyl chloride, hence the low boiling point. In cases of this kind the ether is separated from the ethyl chloride by fractional distillation.[5]

‡ This does not mean that no ether was present. It simply means that probably less than 0.03 cc. of ether was present.

Table 1 indicates that by our method as little as 0.06 cc. of ether in 500 Gm. of tissue can be isolated. It shows further that if tissues contain about 0.3 cc. or more of ether in 500 Gm., the yield of isolated ether is on the average 83.6 per cent (± 5 per cent). If the ether present in the tissues is very small (cases 1 to 6), the percentage yield is much smaller (from 42 to 60 per cent). It will be noticed, however, that the ether lost in the procedure is extremely small (from 0.03 to 0.07 cc.). This loss is relatively large on the basis of percentage. In cases in which the patient dies under full ether anesthesia or as a result of an accidental overdose of ether and in homicides by the administration of ether, the ether in the tissues is always higher than 0.3 cc. in 500 Gm. Therefore, in such cases the yield is good and fairly constant. The direct measurement of the isolated ether can be used for the estimation of the ether actually present in the tissues.

The data in table 2 prove that the ether (in excess of 0.03 cc.) present in tissues as a result of anesthetization can be isolated and measured. Recovered ether in amounts as small as 0.03 cc. can be used for the determination of the microboiling point. The boiling points obtained on the specimens of isolated ether ranged from 34.5 to 35.1 C. These values compare favorably with the theoretical boiling point of ether, from 34.7 to 35 C. The boiling point, therefore, can be used for identifying the ether. Other properties of identification of ether are: It is a thin mobile liquid; it is lighter than water, does not freeze in a solid carbon dioxide-acetone bath, has an ethereal odor, takes fire rapidly and burns brilliantly.

We are drawing no conclusions as to the amount of ether in the brain when a patient is fully anesthetized, because the data are still too meager. Further research is in progress on this phase.

SUMMARY

A micromethod for isolating ethyl ether from human tissues is described. Amounts of ether as small as 0.06 cc. in 500 Gm. of tissue were isolated and measured. In tissues containing from 0.3 to 0.9 cc. of ether in 500 Gm., the recovery is 83.6 per cent (average). The recovery of ether is fairly constant and can be used for estimating the amount originally present in the tissues. Determinations of the microboiling point served to identify the isolated liquid as ethyl ether.

HISTOLOGIC CHANGES IN THE KNEE JOINT WITH ADVANCING AGE

RELATION TO DEGENERATIVE ARTHRITIS

FREDERIC PARKER, JR., M.D.
CHESTER S. KEEFER, M.D.
WALTER K. MYERS, M.D.
AND
RALPH L. IRWIN, M.D.
BOSTON

In a previous article, we[1] discussed the gross anatomic changes observed in one hundred knee joints removed from patients who had died of various diseases. It was stated that erosions occurred with increasing frequency with advancing age, and that the alterations were precisely the same as those previously described by many observers as characteristic of degenerative arthritis.[2] In order to determine whether the anatomic changes were the same histologically as those frequently described in degenerative arthritis, the abnormal areas, the synovial membrane and the capsule were examined microscopically.

Material for histologic study was taken from the synovia, cartilage and bone. Approximately one thousand microscopic sections from these joints were examined. A summary of the results is recorded.

THE SYNOVIAL MEMBRANE

On opening the knee joint, the synovial membrane appeared smooth and glistening in 66 per cent of the cases. The cavity of the joint usually contained a small amount of fluid. In a few instances the synovial cavity of the knee joint communicated directly with that of the tibiofibular joint. This is of practical significance, as an infection of one joint may extend into the other through this direct communication.

As a rule, the synovial membrane showed gross abnormalities only when there were striking alterations in the cartilage and bone. The

---

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), the Department of Pathology, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Keefer, C. S.; Parker, F., Jr.; Myers, W. K., and Irwin, R. L.: Relationship Between Anatomic Changes in Knee Joint with Advancing Age and Degenerative Arthritis, Arch. Int. Med. **53**:325 (March) 1934.

2. In this report, the term "degenerative arthritis" is used synonymously with osteo-arthritis or hypertrophic arthritis.

most common observation was that of papillary projections extending from the surface of the synovial membrane. These were especially numerous and prominent about the edges of the patella, and inasmuch as erosions of the cartilage were more common on the medial than on the lateral patellar facets, the synovial fringes were seen more often at this location. In some cases, these fringes completely filled the depressions caused by erosions; in others, they projected from the surface into the joint cavity, particularly about the region of the semilunar cartilages. In the cases in which the fatty pad was large and abundant, the synovia over the surface projected in small nodules or in fringes, filling in every small part of the joint cavity.

The capsule of the joint was, as a rule, not thickened, although in the cases in which the capsule was stretched the fibrous tissue was extremely tough and of increased density.

Histologically the synovial membrane consisted of loose connective tissue containing elastic fibers and numerous groups of fat cells. Over the surface, the cells were flattened, the thickness of the surface layer being only two or three cells deep. These surface cells were irregularly oval or stellate and closely packed together. The capsule was composed of interlacing thick bundles of dense fibrous tissue which varied in thickness in the different joints. Blood vessels and nerves were found in abundance in the synovia, and some of the nerve fibers had pacinian corpuscles as endings. Lymphatics were likewise seen within the synovial membrane, usually just below the surface.

We have said that in some areas there were projections of the synovial membrane into the joint cavity. They consisted of connective tissue, capillary blood vessels and masses of fat and were covered with layers of synovial cells. In some the surface cells were heaped up in several layers beneath which were many lymphocytes in the connective tissue core. In a few there were perivascular collections of lymphocytes and rarely focal collections of plasma cells. The core in a few of the projections was hyalin in appearance or contained fibrous tissue of variable density.

In the subsynovial layer there were a few lymphocytes, a rare mast cell or a few plasma cells. In a few sections one could see blood pigment in mononuclear cells and dense collagen about the blood vessels. In the larger blood vessels of the joint capsule one frequently observed intimal thickening. The smaller vessels, as a rule, did not show any abnormal anatomic changes, although in a few cases thrombi were observed in the smaller vessels with a few polymorphonuclear cells surrounding them. The case in which obliterative changes were shown in the smaller blood vessels were usually those in which there were stretching of the capsule and extensive anatomic changes in the joints.

Metaplasia of the connective tissue of the synovia and capsule was observed with resulting cartilage and bone formation at various stages of development. This is shown in figure 1.

THE ARTICULAR CARTILAGE

The earliest change was a decrease in basic staining with a tendency toward staining with acid dyes. Associated with this was a development

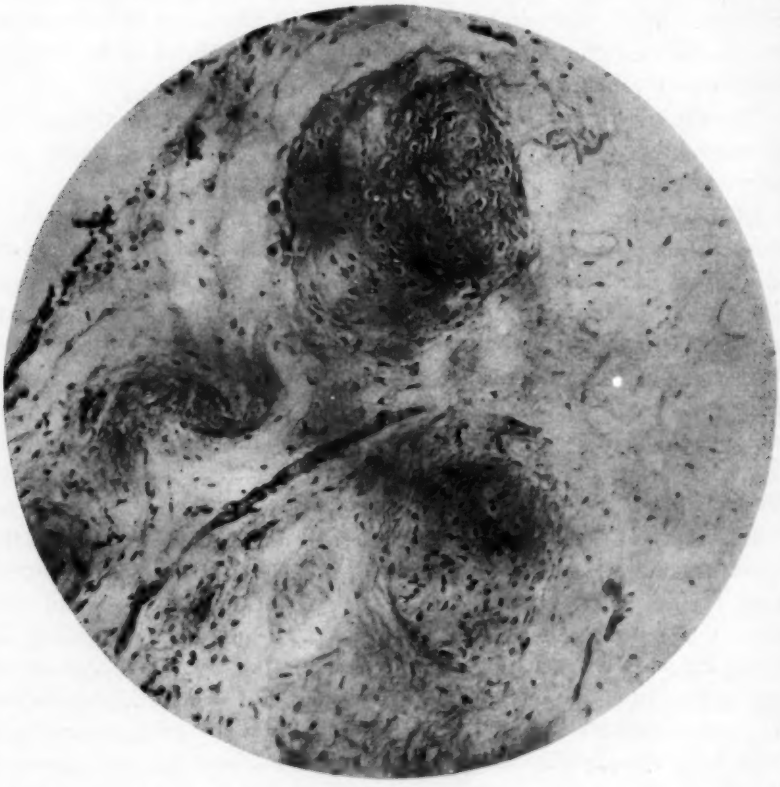

Fig. 1.—Metaplasia of synovial membrane. Islands of young cartilage cells in the synovial membrane; × 110.

of fissures resulting in an irregularity of the surface with papillary projections. In such projections there were roughly spherical groups of ten or more small, young cartilage cells. This process was at first superficial, but later the fissures extended deeper into the cartilage, and here the cells appeared fewer and swollen. With loss of the superficial layers and extension of the process to the subchondral bony plate the normal arrangement and appearance of the deep cartilage cells were lost, and only groups of the small cartilage cells heretofore described were present. Finally, there was complete destruction of the cartilage

with exposure of the subchondral bone. Occasionally the cartilage showed cystic areas filled with mucoid material; in several instances at its junction with the bony plate it contained no nuclei, was granular and definitely necrotic. In such areas erosion of the more superficial layers had occurred. Sometimes when there was erosion of the cartilage the denuded areas were covered with somewhat vascular connective tissue continuous with that of the marrow. Embedded in this tissue were chondroid tissue and fragments of necrotic cartilage surrounded by foreign body giant cells. In rare instances, the connective tissue over the uncovered bone was seen as an ingrowth from the capsule.

Where the bone and cartilage had been depressed below the normal line of the articular surface the cartilage had thickened to fill in the defect, with resulting approximate restoration of the joint line.

CHANGES IN THE BONE

1. *Subchondral Bone.*—The subchondral bone showed increased thickness in areas which were the site of erosions of the articular cartilage, and also where the cartilage and bone had been depressed below the normal articular surface. This bony thickening was due to compression, as indicated by the distortion of the trabeculae, and to formation of new bone. In the areas of thickening the cartilage extended into the bone more deeply than normally. The prolongations resembled normal ones so far as the cartilage was concerned and were quite different from the islands of cartilage subsequently described. In these areas, the blood vessels showed slightly increased perivascular connective tissue, often with slight infiltration by lymphocytes.

In cases in which the destruction of the articular cartilage was marked with frequently accompanying fragmentation of the cartilage and necrosis there was also necrosis of the bone. In some of the lesions of this type new bone was forming and, as a rule, there was a marked increase of connective tissue in the marrow extending up to and over the affected surface (fig. 2). Occasionally small longitudinal fractures of the bony plate occurred with an extension of the articular cartilage between the fragments. In the subchondral bone cysts filled with a mucoid material were not uncommon.

2. *Islands of Cartilage.*—Associated with marked lesions of the articular cartilage, islands of hyaline cartilage were found in the subchondral region. These islands were situated both within the bony trabeculae and on their surfaces. Those within the trabeculae were often irregular; in some instances they were connected with the articular cartilage while in others they were located at some distance from the articular cartilage and showed no apparent connection. The cartilaginous islands on the surface of the trabeculae were, as a rule, roughly

spherical and attached to the bone at one point. They apparently arose in the endosteal layer, for in the earliest stages of their formation a single cartilage cell could be found in this location. The cartilage of which these islands were composed was of the hyaline type with well formed young cartilage cells. Some of the islands on the surfaces of the trabeculae were undergoing ossification, a layer of new bone sur-

Fig. 2.—Island of cartilage in bone marrow pushing aside and compressing the blood vessels. Erosion of cartilage and bone with areas of connective tissue proliferation and new blood vessels in the subchondral area. Formation of new cartilage and bone is present in the subchondral area; × 50.

rounding the cartilage on the side toward the marrow; there was no central ossification such as occurs in exostosis cartilaginea.

The islands in the marrow not connected with bone or with endosteum arose from a metaplasia of the connective tissue of the marrow, a process similar to that noted in the synovia. The earliest stage was a thickening of the connective tissue with the appearance of a few

small cartilage cells embedded in a pink-staining, hyaline matrix. Later these cells increased in size and were surrounded by a dense, hyaline, basically staining substance—chondromucin (fig. 3). At the periphery of such an island containing well developed cartilage cells were young cells similar to those described as appearing first.

3. *Formation of New Bone.*—Formation of new bone was found both at the articular surface and in the subchondral trabeculae. It

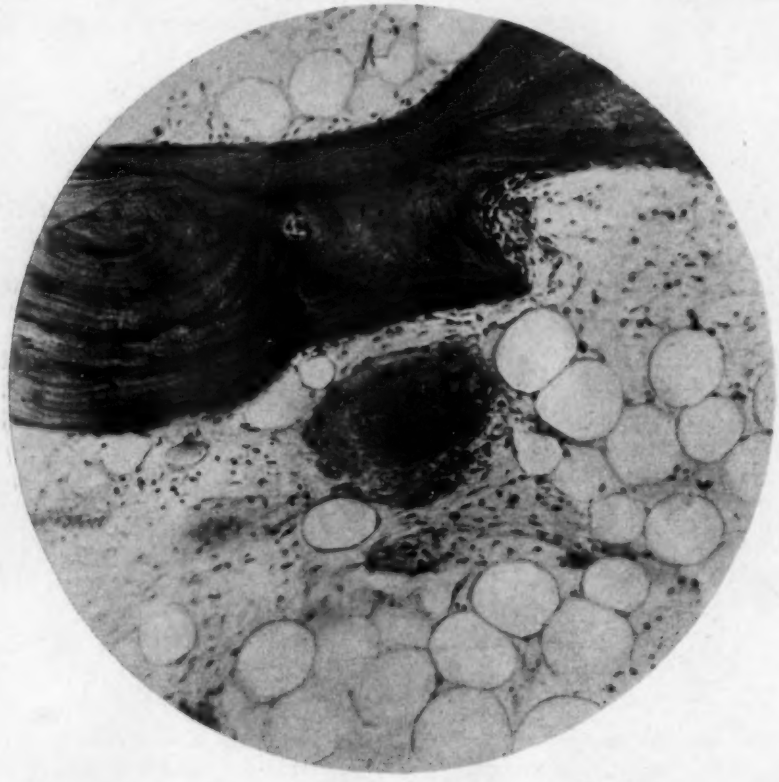

Fig. 3.—Young cartilage cells arising from connective tissue of the bone marrow. They are not attached to the endosteum of the trabeculae; × 110.

occurred at the former site when there had been destruction of the cartilage and bone and was usually accompanied by a proliferation of vascular connective tissue arising in the marrow.

The subchondral bony plate and the underlying trabeculae showed the formation of new bone at the base of erosions and of the aforementioned depressed areas. This bone was formed by the laying down of new bone along the surfaces of the old bone and by the ossification of the islands of cartilage. Wherever the process was active the marrow spaces were filled with vascular connective tissue.

The formation of new bone took place in still another way. In the subchondral bone, extending upward into the overlying cartilage, there could be found islands of vascular connective tissue. Some of these merely consisted of this tissue with osteoclasts lying in its interstices. Others had a peripheral row of osteoblasts while, in still others, ossification of the adjacent cartilage was taking place with the result that such foci of vascularization were partly or entirely surrounded

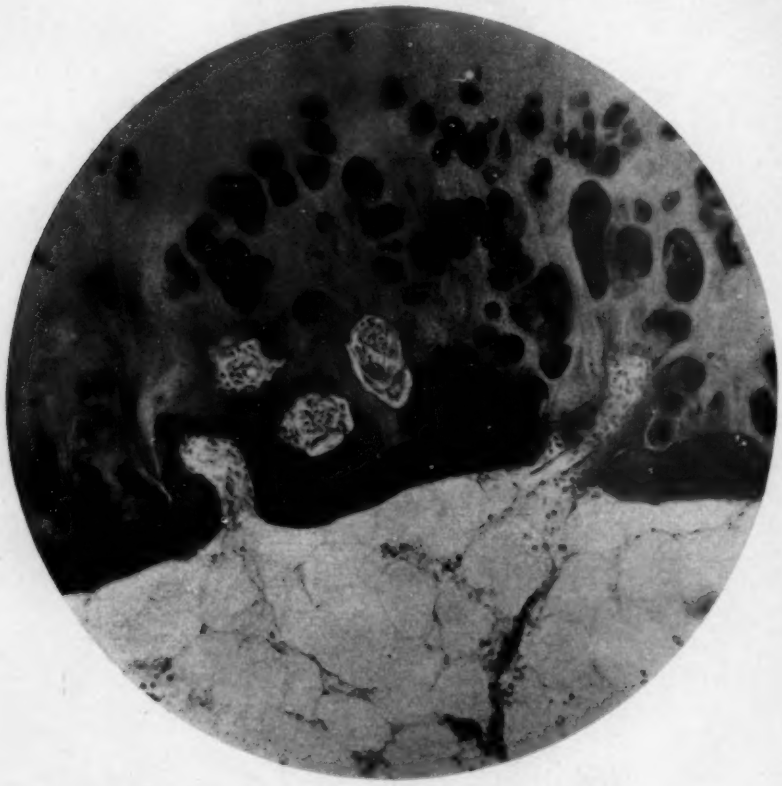

Fig. 4.—Vascularization of the subchondral area. Formation of new bone about one of these areas; × 110.

by bone. As a rule, this new bone was at first unconnected with the subchondral plate; but it eventually became connected with it, appearing finally as a roughly spherical or hemispherical, avascular nodule. The end-result was that the subchondral bony plate showed an irregularly nodular surface instead of the normal smooth line.

In several instances the vessels in these islands of vascularization could be followed into the marrow, and there they lost their sheath of connective tissue (fig. 4).

4. *Fractures.*—Several instances of fractures of the articular cartilage and subchondral bony plate were found. In the most marked case, one portion of the cartilage and bone had overridden the other. The cartilage in both portions was in good condition. Formation of new bone was active on the articular aspect of the depressed cartilage and on the under surface of the subchondral bony plate of the overriding part. The cartilaginous parts of the two portions had made a firm union, leaving no visible line of separation. The joint surface showed a U-shaped depression over this area.

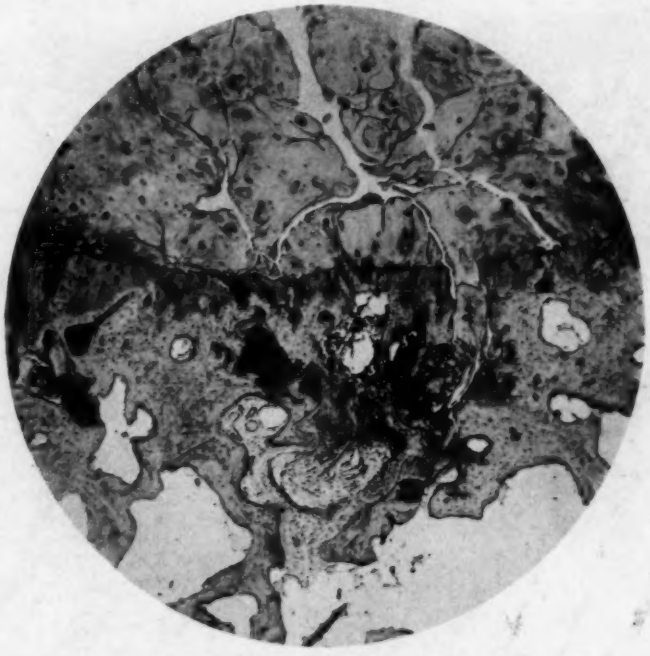

Fig. 5.—Fracture of the subchondral bony plate with articular cartilage forced into the area of fracture. Fragmentation of surface cartilage; × 50.

In several cases, the subchondral bony plate showed small longitudinal fractures with protrusion of the cartilage into the underlying marrow. This condition is illustrated in figure 5.

In one specimen there was a projection of bone in one area above the line of the subchondral bony plate. The articular cartilage was missing and the surface was covered with connective tissue. The bony trabeculae were thickened and the marrow spaces filled with rather dense fibrous tissue. This lesion was interpreted as representing a previous longitudinal fracture with bony repair.

5. *Marrow.*—Where erosion of the articular cartilage had occurred, extending down to and often into the subchondral bony plate, there was,

as a rule, a proliferation of connective tissue in the marrow spaces beneath the eroded areas. This connective tissue at first appeared as a delicate reticular tissue and was usually infiltrated with lymphocytes and a few macrophages. An atrophy of the fat tissue accompanied its appearance. As this connective tissue became older, it grew denser and contained numerous well formed blood vessels. It appeared first in the marrow spaces beneath the subchondral plate, but if the erosion

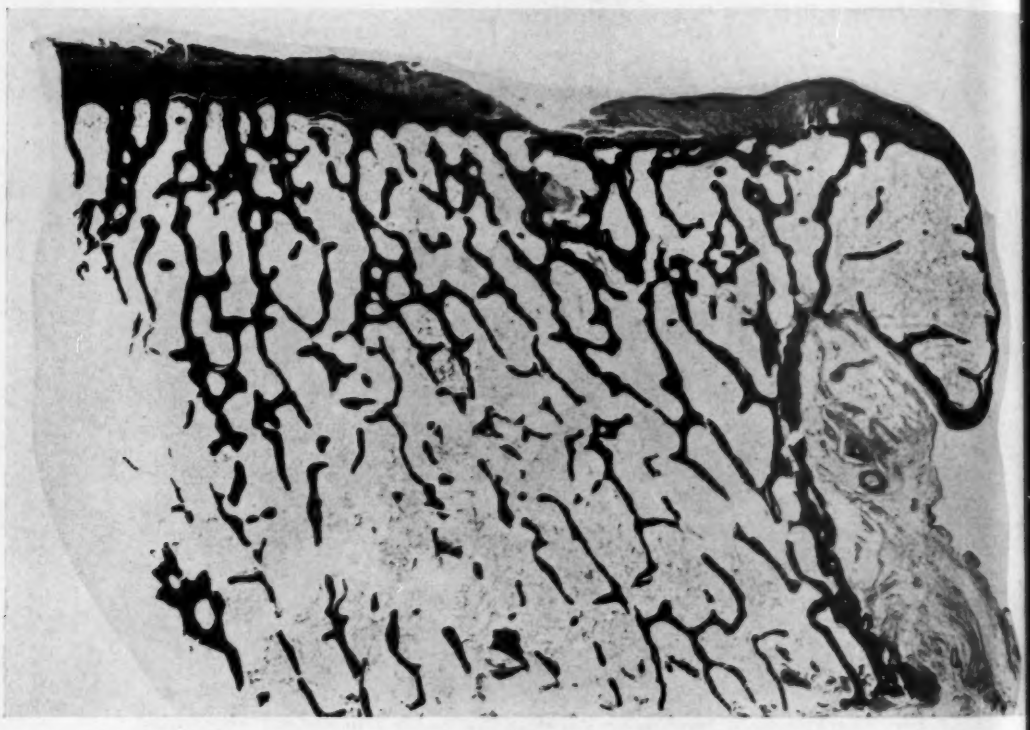

Fig. 6.—Articular surface of the femur showing thinning and fibrillation of the cartilage, flattening of the joint surface and formation of a bony projection ("exostosis") due to forcing of the bone outward; × 25.

was extensive and involved the bone, it extended up to and over the articular surface as well as deeper into the marrow. Not infrequently fragments of dead bone and cartilage could be found embedded in the superficial layers. Cysts occurred in the deeper portions. The fatty tissue underwent atrophy as the connective tissue proliferated and also in certain instances degenerated and became necrotic as evidenced by collections of macrophages arranged peripherally around the fat cells.

Rarely was any blood-forming tissue present in the marrow; when it occurred, it was in small amounts.

Vascular changes, that is, intimal thickening, were frequent, but no specific changes in the surrounding tissue could be associated with them.

6. *Exostoses.*—A considerable number of our specimens in which there was flattening of the joint surface showed projections at their peripheries. These projections consisted of fatty marrow, trabeculae of bone and a layer of bone continuous with the subchondral plate (fig. 6). They were partly covered with articular cartilage and partly with connective tissue which could be followed into the capsule of the joint.

The marrow was essentially normal, although at times it showed infiltration with a few lymphocytes. No proliferation of connective tissue and no islands of cartilage were noted in the marrow of the projections.

The bony trabeculae were made up of well formed, dense bone. Their long axes were either parallel with or at right angles to those of the trabeculae of the epiphysis. No evidence of a formation of new bone was present.

The covering layer of bone was, as aforesaid, a continuation of the subchondral plate. In a number of instances, however, there was evidence of a formation of new bone and a destruction of bone in this peripheral region. The new bone was for the most part formed on the endosteal side, but sometimes the periosteum also took part in the process.

The cartilaginous portions of these projections were continuous with the articular cartilage and resembled the latter in every respect.

Occasionally, the projections were vertical, that is, at right angles to and projecting above the line of the joint surface, but usually they were parallel to the articular surface and in shape suggested a rolled-over edge of the joint surface.

Islands of bone and cartilage occurred occasionally in the connective tissue of the joint capsule and in the attachments of the tendons.

COMMENT

It has been repeatedly shown that the characteristic lesions in degenerative arthritis are: (1) changes in the cartilage such as fibrillation, erosion and destruction with attempts at regeneration; (2) alterations in the subchondral bone due to increased vascularization, ossification, fracture, attempts at repair with formation of new bone, islands of cartilage and cysts in the cancellous bone, and (3) the formation of exostoses, sometimes called lipping, "Randwülsten," etc. The term "hypertrophic arthritis" has been applied to this condition on account of the increased density of the bone and overgrowth of the cartilage. We believe that these processes result from the repair occurring in damaged cartilage and bone and are not primary lesions

of the joints. We have arrived at this conclusion as a result of the study of the gross and microscopic changes in the joints detailed in the foregoing sections. Inasmuch as it is important to establish whether these changes are primary or whether they result from attempts of the parts to repair the damage done by wear and tear, the changes we have observed require special comment.

Changes in the Cartilage.—In the gross description of the joints, we described the early changes observed in the cartilage. These changes were characterized by a fragmentation of the cartilage in the vertical plane so that the surface had an irregular and uneven appearance, resembling the pile of a woolen rug. Following this fibrillation, the cartilage was frequently worn away so that the underlying subchondral bone was exposed. Often one observed evidence of regeneration of the cartilage, but at best this was not striking, probably owing partly to the poor regenerative powers of cartilage and partly to the movement which takes place in such joints. Many of the areas of cartilage showing regeneration were similar to those observed experimentally in animals by Bennett, Bauer and Maddock,[3] thus demonstrating that hyaline cartilage may regenerate in man as well as in animals.

Islands of Cartilage.—In common with other observers, we have found islands of cartilage cells in the marrow at some distance from the joint surface. The origin of these cartilaginous areas has been the subject of many controversial discussions. As a result of a study of many cases, Pommer[4] and Lang[5] concluded either that they were due to emboli of cartilage cells which were carried to the marrow by the blood vessels or lymphatics or they arose from microscopic fractures in the cancellous bone. Heine[6] expressed the opinion that many of these islands arose from cartilage that had been forced "durch Einpressung" into the subchondral bone.

Both Pommer and Lang based their conclusions on the observation that these islands were found in the lumens of canals, in the callus that followed fractures of the subchondral bone and in areas that they interpreted as being within blood vessels or in the perivascular lymphatics.

We have considerable anatomic material bearing on the origin of these islands of cartilage as they were seen in the sections from the knee joints. We observed that in the areas where there were fractures in the subchondral plate cartilage was frequently depressed between the edges of the fracture (fig. 5), so that it is possible that in some cases the areas of cartilage in the subchondral bone have such an origin.

---

3. Bennett, G. A.; Bauer, W., and Maddock, S. J.: Am. J. Path. **8**:499, 1932.
4. Pommer, G.: Virchows Arch. f. path. Anat. **263**:434, 1927.
5. Lang, F. J.: J. Bone & Joint Surg. **14**:563, 1932.
6. Heine, J.: Virchows Arch. f. path. Anat. **260**:521, 1926

However, the islands of cartilage in the subchondral bone arise more often from the endosteal layer of bony trabeculae (fig. 7). This is also true when they are located some distance from the subchondral area. In other cases, islands of young cartilage arising from the connective issue of the marrow (fig. 3) may be found, having no connection with the endosteum. These islands of cartilage may also arise from the connective tissue of the callus which forms following small fractures

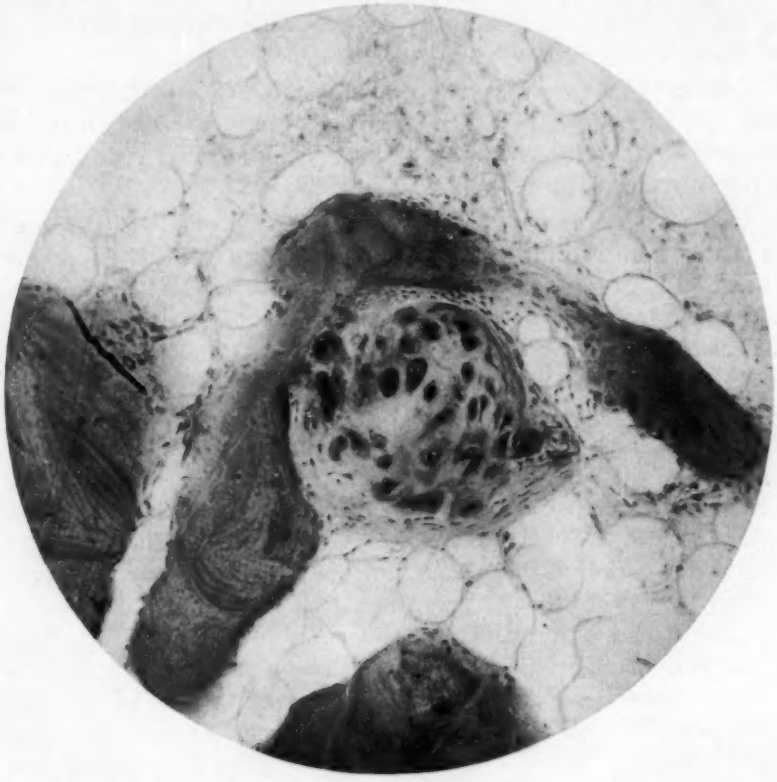

Fig. 7.—Island of cartilage arising from the endosteum of bony trabeculae of the epiphysis; × 110.

in the subchondral area. These islands differ in origin from the ones heretofore mentioned in which the cartilage extends through a fracture of the joint surface. The islands formed from the connective tissue of the callus are situated at some distance from the joint line.

We have examined many sections for evidence that these islands of cartilage develop from small emboli in the blood vessels or perivascular lymphatics as postulated by Pommer. We have not observed any which we could with assurance classify as arising from the blood vessels or

lymphatics. Indeed, in some of the sections islands of cartilage were found developing outside the blood vessels and compressing or pushing aside the vessels as they grew (fig. 2).

From our observations, then, it seems abundantly clear that the islands of cartilage may arise in any one of the following ways: (1) as a result of fracture of the subchondral bone with formation of callus and connective tissue; (2) from the endosteum of the bony trabeculae of the epiphysis; (3) from the connective tissue of the marrow through metaplasia. We were unable to find evidence that they arose from emboli in the blood vessels or lymphatics.

As these islands were observed only in joints in which there was extensive damage to the articular cartilage or to the underlying subchondral bone, it seems fair to assume that they represent a process of repair rather than a primary lesion.

Exostoses.—It has long since been generally admitted that one of the characteristic features of degenerative arthritis is the development of exostoses at the margins of the joint surfaces. Indeed, many observers have regarded their presence as necessary before the diagnosis can be accepted. The origin of these bony protuberances has been an occasion of considerable discussion. They have been described as ossified excrescences, as periosteal or perichondrial proliferations, as osteophytes or as exostoses formed by depression and bending over of the tissue at the edge of the joint surface. Pommer, Lang and others have stated that they arise as outgrowths from the subchondral bone, possess a laminated structure and are usually covered with new cartilage. They admit, however, that the periosteum may show bony proliferation covered by new cartilage at the insertions of tendons, and that it is common to find a formation of new bone in the tendon attachments themselves. This condition is illustrated in children in whom there is increased tension of the muscle tendons at the points of attachment to the bone; excrescences occur at those sites. The same phenomenon may be observed in the osteophytes on the ilium in osteo-arthritis of the hip joint. In the knee joint, however, lipping occurs not only at points which are the sites of attachment of muscle tendons but also at the margins of the patella, femur and tibia.

From our observations on the knee joint we have become extremely skeptical as to whether all these exostoses at the margins of the joint surfaces are really the result of a formation of new bone arising from the subchondral space. We have considerable data bearing on this point. When the joint surfaces and the subchondral areas of a normal joint are compared with those of one showing exostoses, several distinctions are evident. In the first place, exostoses are seen in a joint which is the site of damage or in which the surfaces have not been

mutually adapted to one another. The joint surface is frequently flattened. This is especially striking in a joint in which there is a displacement of the patella either medially or laterally. The bony projections often suggest a mushroom and seem to have been forced outward as a result of the flattening of the joint surface. That is to say, as the normal convex surface of the femur is worn away, the cartilage disappears over the area of pressure and movement, the subchondral bone thickens, and the area of pressure becomes flattened, less convex and, indeed, in some cases depressed below the previous normal line. This flattening of the surface which is in contact with the opposing joint surface causes the edge of the bone to project outward as a shelf, and, depending on weight, pressure and position, the projection may curl or bend over at the edge. These bony prominences are not the result of new growth of bone in every instance, although in the subchondral layer of some of the projections slight evidence of a formation of new bone may be seen as in other subchondral areas. The trabeculae of the projections are either continuous with the cancellous bone or, at the sites where they project over the edge, at right angles to it. We have not found a double layer of cartilage, such as that described by Pommer, Nichols and Richardson,[7] to indicate that the projections result from perichondral or subchondral proliferation. We have searched numerous sections for a double row of cartilage cells without success. In examining numerous gross specimens we found several in which the bony projections curled over at the edge. At first glance it might appear that these represented layering such as has been described. On closer inspection, however, it could be shown that this was not the case and that the double layer of cartilage was due to a projection of the bone and cartilage over the edge of the joint surface. It should be emphasized that the cartilage projects over the edge of the joint surface to a considerable extent in some normal joints so that the variations cause differences in the appearance of the projections.

We believe, therefore, that these bony projections, commonly called exostoses, are areas of bone and cartilage occurring at the edge of the joint surface. They become prominent and conspicuous when the surface of the bone has been altered and flattened, so that the bone and cartilage are forced outward and downward. If, on the other hand, there is a depression of the bone near the edge of the joint surface, the peripheral portion of the joint surface may appear to project above the surface. We found no evidence that these lesions were primary, and we regard them as a part of the change that takes place in distorted joints following alterations in the joint surface near the edge.

7. Nichols, E. H., and Richardson, F. L.: J. M. Research **21**:149, 1909.

Subchondral Bone.—Frequently one of the earliest changes observed in these joints was in the subchondral bone. Pommer was the first to point out that one of the characteristic lesions of degenerative arthritis was an increased vascularization and bony thickening of the subchondral plate. In discussing this phenomenon he stated that the loss of the protection which the subchondral bone received from the cartilage when it lost its elasticity or was destroyed resulted in subchondral thickening with formation of new bone. Nichols and Richardson also described changes in the epiphyseal end of the bone in the cases in which the surface cartilage was destroyed and, also, alterations in the base of the articular cartilage in cases in which the surface was damaged. We have

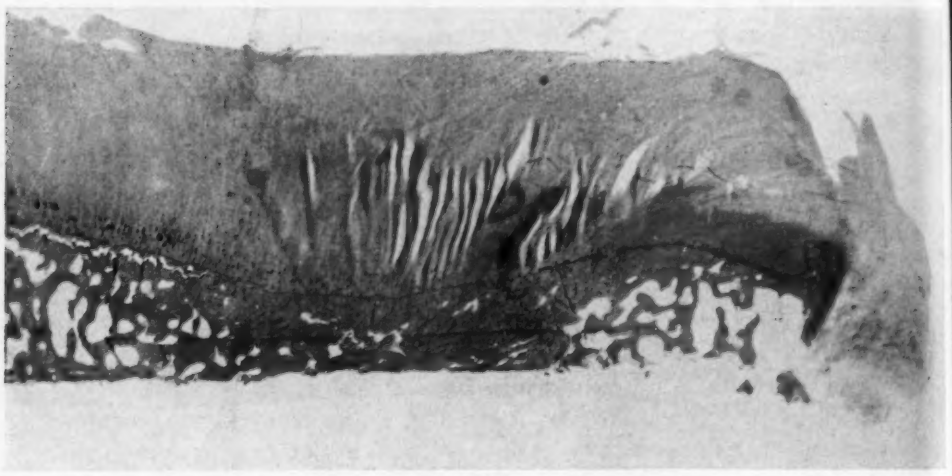

Fig. 8.—Early lesions showing fibrillation of cartilage with compression of the underlying bony trabeculae; × 50.

frequently observed that one of the earliest changes that occurs in the subchondral bone is a compression of the trabeculae due to loss of elasticity and fibrillation in the overlying cartilage (fig. 8). In some of the areas of this type there may be little or no evidence of a formation of new bone; in others, a formation of new bone is obvious.

In addition to such bony changes we observed various stages of the aforementioned vascularization. The earliest stage of this process consists in the appearance in the subchondral bony plate of islands of vascular connective tissue. The vascular tissue extends from the bony plate into the adjacent articular cartilage. One gains the impression that the islands at first cause solution of the surrounding bone and cartilage; osteoclasts are often present. At a later stage osteoblasts appear and, associated with these, ossification of the neighboring

cartilage takes place, a narrow layer of new bone being formed around the island. As time goes on the bone becomes thicker, the connective tissue and blood vessels disappear, and finally there remains a nodule of well formed bone. At first, this new bone is usually unconnected with the subchondral plate, but later it fuses with the plate. When such a process has healed, the upper surface of the plate presents a series of nodules of bone projecting into the base of the articular cartilage. It is difficult to determine the mode of origin of these islands. While it is often possible to trace a blood vessel from such an area into the marrow, we do not believe that there is definite proof that the islands arise from invasion of the bone and cartilage by vessels from the marrow. Such vessels, as a rule, do not show in the marrow the sheath of connective tissue which they possess in the bone and cartilage. It would seem equally reasonable to suppose that these vascular islands arise by a proliferation of connective tissue around vessels preexisting in the bone. Accompanying this proliferation there is a solution of the adjacent bone. Then this vascular tissue penetrates the cartilage and later leads to ossification of the cartilage.

Where erosions of the cartilage have occurred with exposure of the bony surface, thickening of the bone takes place owing to formation of new bone. The new bone is formed by being laid down on the old bone and also by ossification of the islands of cartilage mentioned elsewhere. Accompanying the formation of new bone there is a proliferation of connective tissue arising in the marrow and extending to the subchondral plate. Where destruction of bone, as well as of cartilage, has occurred, this connective tissue extends up to the articular surface, thus filling in the defect.

We view these changes in the subchondral bone as a reaction to the loss of elasticity in and damage to the overlying cartilage. It is really a process of repair or an attempt on the part of the bone to strengthen areas subjected to increased pressure. In view of these alterations occurring in joints which are the site of degenerative changes, one should be extremely cautious in interpreting them as a part of the essential pathologic picture in joints which are the site of proliferative processes. More will be said about this matter when we discuss the pathologic changes of proliferative (rheumatoid) arthritis in a subsequent communication.

In view of our studies it is justifiable to say that the changes which occur in the joints with advancing age are similar, both grossly and microscopically, to those that have been described as being characteristic of degenerative arthritis. We feel that the anatomic changes are caused by injury to the various tissues of the joint and that the final anatomic picture is due to a combination of alterations produced by injury and repair. We believe the sequence of events to be as follows: fibrillation

and thinning of cartilage, compression, vascularization with formation of new bone in subchondral bone, formation of fibrous tissue, of islands of cartilage and of cysts in the bone marrow, and formation of bony projections at the edge of the bone owing to alteration of the joint surface forcing the bone and cartilage outward.

SUMMARY AND CONCLUSIONS

Histologic examination of the tissues from one hundred knee joints of patients who had died of miscellaneous diseases was made. The following points were brought out.

1. The synovia was essentially normal except in cases in which there were alterations in the cartilage. In these the capsule was somewhat thickened, papillary projections of the synovia occurred, and occasionally there were small collections of lymphocytes about the blood vessels.

2. The cartilage showed fibrillation, degeneration and some areas of regeneration. In some cases it was completely destroyed.

3. The subchondral bone was thickened owing either to compression or to formation of new bone. The marrow spaces were frequently filled with fibrous tissue, cysts and areas of cartilage.

4. Bony projections, or so-called exostoses, were due to a projection of bone and cartilage over the edge of the joint surface, or to a depression of the cartilage below its original level, thus giving the appearance of bony outgrowth. They resulted from a forcing outward of bone and cartilage by flattening of the joint surface owing to pressure and erosion.

5. These changes are identical with those previously described as characteristic of degenerative arthritis. The evidence is that they are the result of injury and repair and that they occur with increasing frequency with advancing age.

SUBCUTANEOUS TUBERCULOID LESION OF CATTLE

A MORPHOLOGIC STUDY

WILLIAM H. FELDMAN, D.V.M., M.Sc.
Assistant Professor of Comparative Pathology, the Mayo Foundation
ROCHESTER, MINN.

The true character of the so-called skin lesion of cattle sensitive to tuberculin is still obscure. Although it is generally agreed that the histologic structure of many of these lesions has a marked resemblance to that of lesions of tuberculosis, the evidence advanced to this time is by no means sufficient to prove that Mycobacterium tuberculosis is the responsible etiologic agent.

Many workers have investigated these lesions, but the majority of the published reports have been concerned with the bacteriologic phase of the problem. Efforts have been made to isolate by cultural methods and by inoculation of animals an organism of etiologic significance, and relatively little attention has been directed to the morphologic aspects of the lesions.

About three years ago a project was outlined for the purpose of making a comprehensive study of the morphology of this condition. It was the intention to secure lesions from cattle in as many different parts of the United States as possible and to include in the study specimens from Canada, Mexico, South America and Europe. When the material was being collected, a paper by Runnells [1] was published in which were recorded the results of a detailed study of the pathologic histology of the so-called skin lesions. Runnells' fifty-six specimens were secured from fifty animals from six widely separated sections of the United States and Canada as follows: seventy-two from Michigan, six from Arizona, eight from California, five from Montana, three from New York, eleven from Iowa and one from Quebec.

Runnells' study seemed to make additional research on morphology superfluous, and the project was abandoned for the time being. However, specimens continued to be received from different parts of the United States, and an opportunity was presented to conduct additional studies on the bacteriologic aspect of the problem. Consequently, because of the amount of data that eventually has accumulated, it seems desirable to make available for others certain conclusions concerning the character of this rather commonly encountered condition.

From the Institute of Experimental Medicine, the Mayo Clinic.

1. Runnells, R. A.: J. Am. Vet. M. A. **81**:173, 1932.

SOURCE OF MATERIAL

Requests for specimens were addressed to Inspectors-in-Charge of the Federal Meat Inspection Service, Bureau of Animal Industry, United States Department of Agriculture in various parts of the United States, who secured material from animals slaughtered under their supervision. Fifty specimens were secured from twenty-one states as follows: Alabama, two; California, two; Colorado, three; Georgia, one; Idaho, four; Illinois, five; Indiana, one; Iowa, three; Kansas, two; Maryland, two; Michigan, two; Minnesota, four; Nebraska, two; New Jersey, one; New York, six; Oregon, two; Pennsylvania, one; Utah, three; Vermont, one; Virginia, two, and Wisconsin, one. One specimen was received from Dr. C. A. Mitchell, Ottawa, Canada. Attempts to secure material from Mexico, South America and Europe, including the British Isles, were unsuccessful. Whether the subcutaneous nodules appear only in cattle in the United States and Canada is not certain, although correspondents in Continental Europe and the British Isles were of the opinion that such lesions occur seldom if ever in the cattle of that part of the world.[2]

All animals from which the subcutaneous lesions were obtained had previously revealed sensitivity to tuberculin administered intradermally. The respective specimens were removed from the carcasses during postmortem examination, were placed immediately in a dilute solution of formaldehyde, U. S. P. (1:10), and were mailed to the laboratory. Lesions were secured only from animals which had no other gross lesions which might have been considered tuberculous. With few exceptions the lesions were confined to the subcutis of the lower extremities and were characteristic of the usual entity designated by federal meat inspectors as "skin lesions."

METHODS

Histologic sections were prepared from each of the lesions and stained with hematoxylin and eosin. Sections from all lesions were also stained appropriately with carbol-fuchsin to reveal the presence of acid-fast bacteria that might be present. In addition, sections from the more representative lesions were stained for reticulum by the method of Pap.[3]

---

2. In a brief report by Fischel (Wien. tierartzl. Monatschr. **15**:423, 1928) mention is made of the finding of twelve cases of tuberculosis of cutaneous and subcutaneous tissues among a total of 2,100 cattle slaughtered at St. Marx. Smears revealed acid-fast bacillary forms in several of the lesions, and the tuberculous character of the condition was definitely apparent in sections prepared from the diseased tissues. With one exception the regional lymph nodes were not tuberculous, and in only two instances was there tuberculosis elsewhere in the body. It was not mentioned if efforts had been made to determine the etiology of the lesions by culture or by inoculation of animals, so the exact type of the lesions reported by Fischel remains a matter of conjecture.

3. Pap, Tibor: Centralbl. f. allg. Path. u. path. Anat. **47**:116, 1929.

PATHOLOGIC ANATOMY

Gross Appearance.—Few of the lesions obtained actually involved the dermis. The irregular nodular masses, which varied in size from less than 1 cm. to as much as 4 cm. in diameter, were definitely situated in the corium and underlying subcutaneous tissues, often extending from the epithelial layer to the musculature. One somewhat unusual specimen consisted of a compact, elongated mass of granulomatous tissue 3 cm. thick and approximately 20 cm. long. Many of the nodules were irregularly spherical, and others were of a flattened, ovoid shape. All were invested with a tough, indistinct, fibrous capsule which provided a rather firm attachment to the adjacent tissues. On incision mineral salts were revealed in thirty-three of the fifty-one specimens studied. The amount of calcification was variable, but was often sufficient to require decalcification of the tissue before sections could be prepared.

The lesion proper varied in appearance. Some lesions consisted of single, purulent or caseous yellowish abscesses, with dark, hemorrhagic, peripheral zones, but the majority of the lesions were composed of proliferative elements the continuity of which was often interrupted by multiple necrotic foci. The necrotic foci of some nodules were small and extremely numerous, whereas in others two or three foci constituted the lesion. Occasional lesions were observed in which necrosis could not be detected with the unaided eye. These were characterized by appearing to be composed of proliferating tissue elements not unlike new growths. The necrotic content of the various foci varied from a semidry, caseous material to a material that was pasty or even purulent.

Pathologic Histology.—Histologically, the material studied could be separated into two general groups. In one group there was a monocytic and epithelioid reaction such as to justify the presumption that a common or closely related provocative agent was responsible for the morphologic changes. These lesions were tuberculoid, with a resemblance to the lesions of genuine tuberculosis that was remarkable in some instances. The lesions constituting the second group were frankly pyogenic, with nothing in common with those in the first group except the situation in which they occurred. Thirty-four of the specimens were tuberculoid, and fourteen were considered nonspecific pyogenic abscesses. Two of the specimens revealed only hyperplasia of the corium without any specific changes, and one of the nodules was diagnosed histologically as an adenoma of the sebaceous glands (adenoma sebaceum).

Since the central portion of the lesion often has a tendency to undergo necrosis, it is imperative that the character of the cells at the periphery be taken into account in studying the histopathologic characteristics of the disease. Although the bulk of the structure may have undergone

necrosis, and few intact cells may remain, there is usually a narrow peripheral zone in which cells characteristic of the lesion can be observed.

The lesions to which I have referred as tuberculoid are subject to considerable variation in histologic appearance, but all have a peripheral zone of monocytic or epithelioid cells which are of the greatest significance in recognizing a given lesion.

In general, the structural design is of two types, and although a given subcutaneous nodule may reveal exclusively one or the other, it is not uncommon to find in some lesions both varieties of morphologic expression.

In one variety of lesion the histologic picture is strikingly reminiscent of the typical lesion of tuberculosis. The tubercle-like structures occur as single or multiple, lobulated units with a peripheral zone of connective tissue (figs. 1 and 2). The cellular elements of such a structure consist of a predominance of monocytic cells which often reveal a tendency to assume an epithelioid appearance. The epithelioid cells are more numerous toward the center of the lesion, where necrosis is commonly a prominent feature. The necrosis is usually caseous. In the outer zone of a tubercle of this kind variable numbers of lymphocytes occur, and numerous small vascular channels are not uncommon. Giant cells of the Langhans type are present, often in abundance, in the majority of lesions.

The histologic appearance of the lesions just described is subject to considerable variation, depending apparently on the duration of the disease. Not infrequently an aggressive, proliferative type of the disease is encountered in which the nodules of monocytic cells are small and extremely numerous, with but little if any necrosis apparent. Mineral salts are often discernible in lesions in which there is considerable necrosis, but may be absent.

In contrast to the multiple, well defined, tubercle-like structures that characterize the lesions just described, considerable numbers of lesions occur in which the pathologic characteristics are somewhat different. The difference, however, is one of dimension rather than of the cellular elements involved. Lesions of the latter type are characterized by the occurrence of extensive, irregular, more or less diffuse areas of necrotic débris, surrounded by a rather narrow peripheral zone of well differentiated epithelioid cells supported by variable amounts of connective tissue, many of the strands of which extend for a considerable distance between the epithelioid cells at right angles to the peripheral capsule (fig. 3). In some instances the necrosis of the lesion has advanced so as to include practically all of the cellular elements within the surrounding capsular investment, and calcification is often excessive. Giant cells of the Lang-

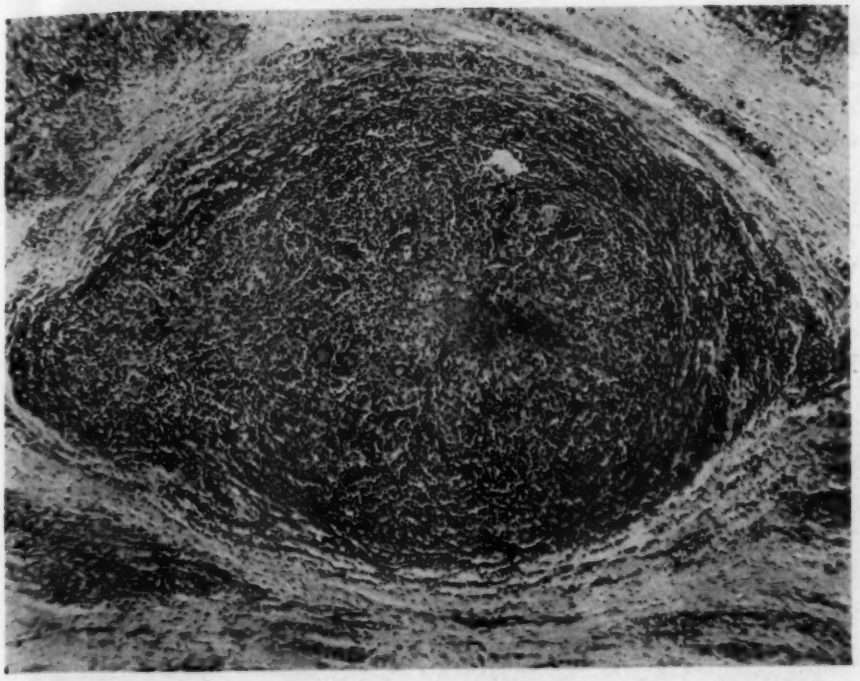

Fig. 1.—Tubercle-like lesion of the subcutaneous tissues with beginning necrosis of the central portion; × 45.

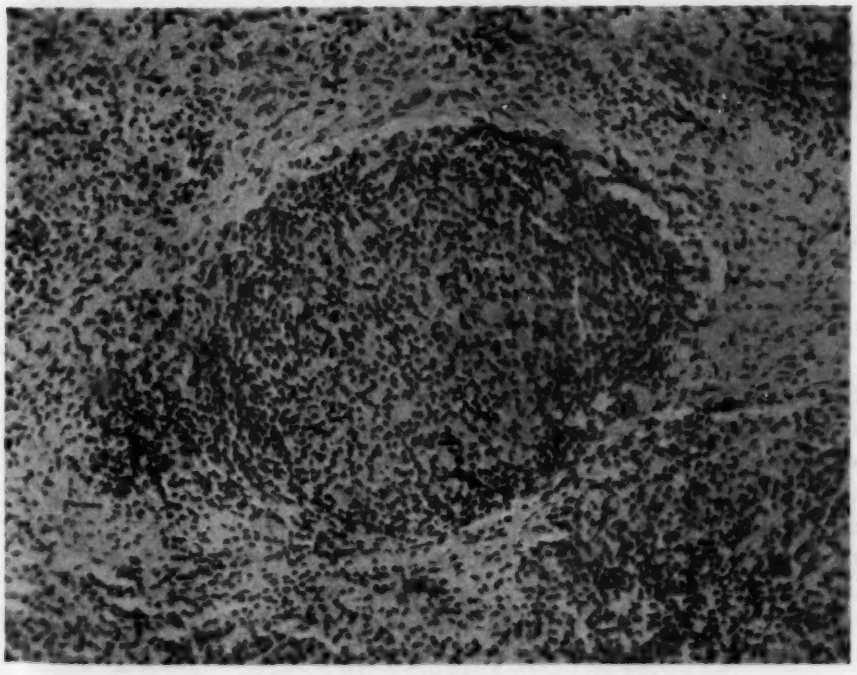

Fig. 2.—Small early proliferative tuberculoid lesion composed largely of monocytic cells with peripheral lymphocytic infiltration; × 130.

hans type, which are rather numerous in the tubercle-like lesions first described, are rare in the larger and more necrotic variety of lesion.

Sections stained by Pap's method revealed an elaborate reticular system as an integral part of the respective cellular reactions (fig. 4). The reticulum fibrils were most numerous in those tubercle-like units which were in a progressive state. In the larger lesions, in which considerable central necrosis had occurred, the reticulated meshwork had disappeared. The reticulum was best observed in the smaller tubercle-like structures in which there was an abundance of epithelioid cells.

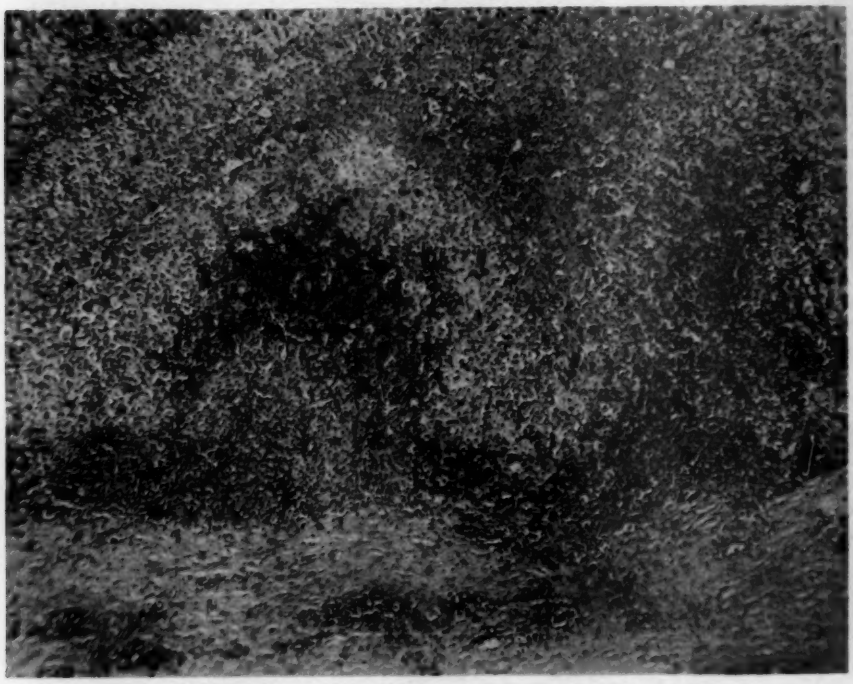

Fig. 3.—Diffuse monocytic and epithelioid cellular reaction with extensive necrosis of a lesion from the subcutaneous tissues; × 45.

Here the intricate meshwork of the extremely fine, threadlike, tapering fibrils was indeed striking. The fibrils extended in every direction, but seemed to have their origin in cells near the periphery. These structures were never seen in areas of necrosis even in the smallest tubercle-like units, and were not observed within giant cells of the Langhans type. In some lesions well developed reticulum fibrils could be seen surrounding each epithelioid cell, whereas in others the fibrils surrounded groups or packets of several cells. The reticulum was not unlike that seen in the tubercles of true tuberculous infections of other tissues.

In no instances in the material examined did the proliferative and necrotic process extend into the substance of the musculature, although lymphocytic infiltration frequently was observed between the muscle fibers adjacent to the lesions in the subcutaneous tissues. As a consequence of the increased pressure, many of the muscle fibers in the zone immediately adjacent to the tubercle-like formations were compressed and atrophic.

The changes involving the blood vessels, mentioned by Carpenter and Goldberg,[4] and by Runnells, were often present in the material

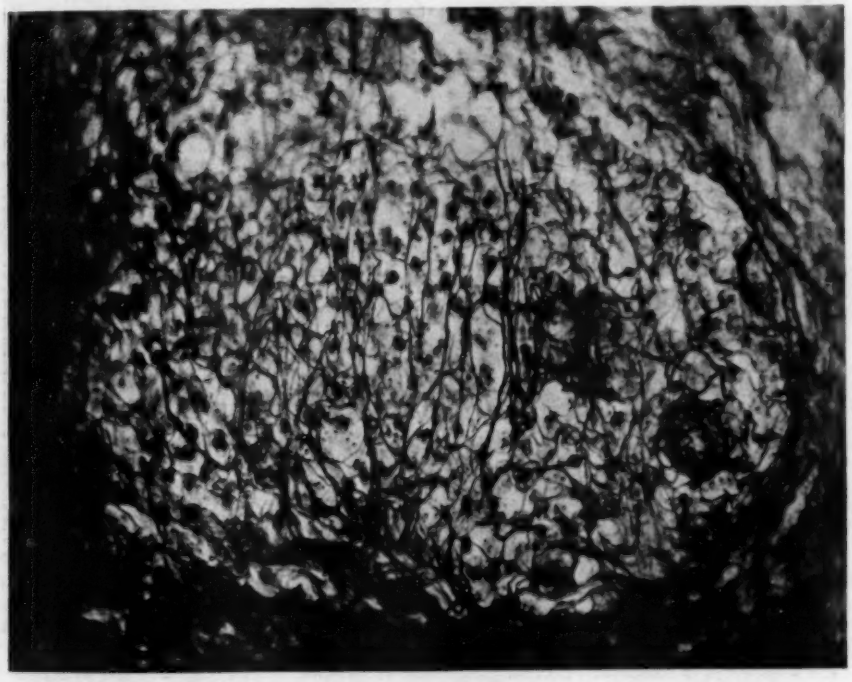

Fig. 4.—Epithelioid tubercle-like reaction stained to reveal the fibrillar reticulum; subcutaneous lesion; × 440.

studied. These consisted of perivascular infiltrations, particularly noticeable around the smaller vessels in the corium (fig. 5). The cellular elements were largely monocytic, with few lymphocytes noticeable. It was not uncommon to observe well established changes affecting the lining of blood vessels. The proliferative endarteritis, affecting the entire intima, caused marked narrowing of the lumen, and not infrequently almost complete obliteration of the lumen resulted. A few vessels were observed that contained canalized, thrombus-like obstruc-

4. Carpenter, C. M., and Goldberg, G. A.: Cornell Veterinarian **15**:148, 1925.

tions. The character and extent of the vascular changes in much of the material studied were such as to convince me of the significance of the vascular tracts in the genesis of the ultimate tuberculoid lesions. It seems logical to believe, as Runnells pointed out, that the provocative agent entered the subcutaneous tissue through the dermis and followed the perivascular tissue to the depths of the corium and beyond.

Acid-fast bacillary forms were seen in twenty-two of the thirty-four specimens that were considered tuberculoid. The organisms, when

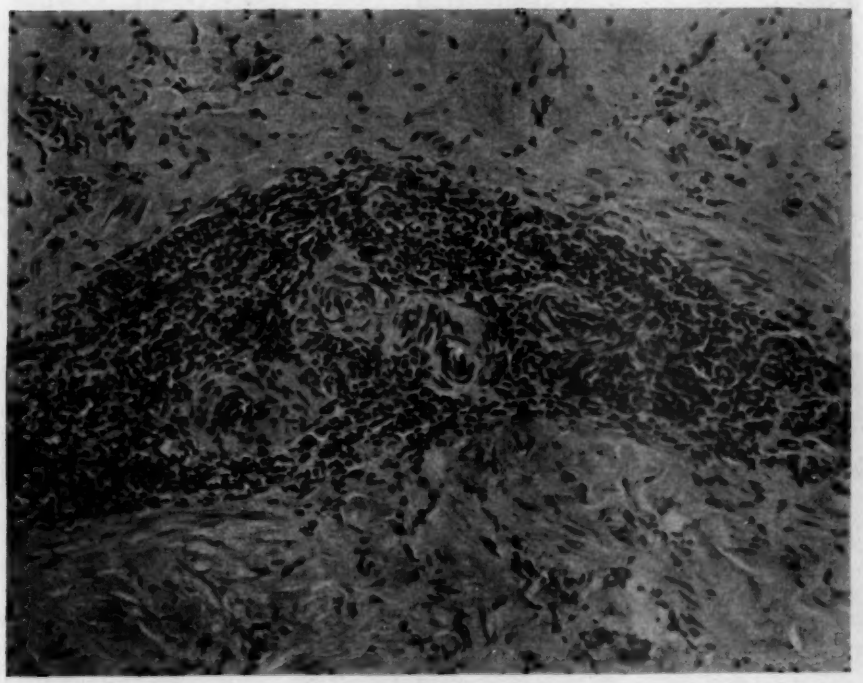

Fig. 5.—Perivascular reaction consisting largely of monocytic cells and lymphocytes. Thickening of the vascular walls and narrowing of the lumens may be noted; × 150.

present, were discernible usually among the cellular débris of the necrotic portion of the lesion. In the aggressive or actively proliferative tissue of the lesion, acid-fast bacteria were seldom numerous and were generally found with difficulty if at all. The organisms varied greatly in number and somewhat in form. In some preparations only two or three bacteria could be found after prolonged search, whereas in others acid-fast forms were exceedingly numerous (fig. 6). There was no question about their acid-fastness, although often shadowy, nonacid forms could be seen lying in the cellular débris. The acid-fast bacteria often have a beaded appearance, with polar and metachromatic granules retaining the fuchsin stain while the vacuolar areas are unstained.

From the characteristic cellular changes of these lesions, the development or pathogenesis of the condition would seem in general to be about as follows: The provocative agent penetrates the dermis through a break in the continuity of the surface portions of the integument. Once in the corium the infective agent, if in proximity to blood channels, incites a cellular reaction composed largely of mononuclear cells, lymphocytes and a few polymorphonuclear leukocytes. This occurs in the tissue elements immediately adjacent to the adventitia in which progenitors of the monocytic cells are found, although some such cells undoubtedly are derived from the blood stream. As the organisms multiply, the cellular

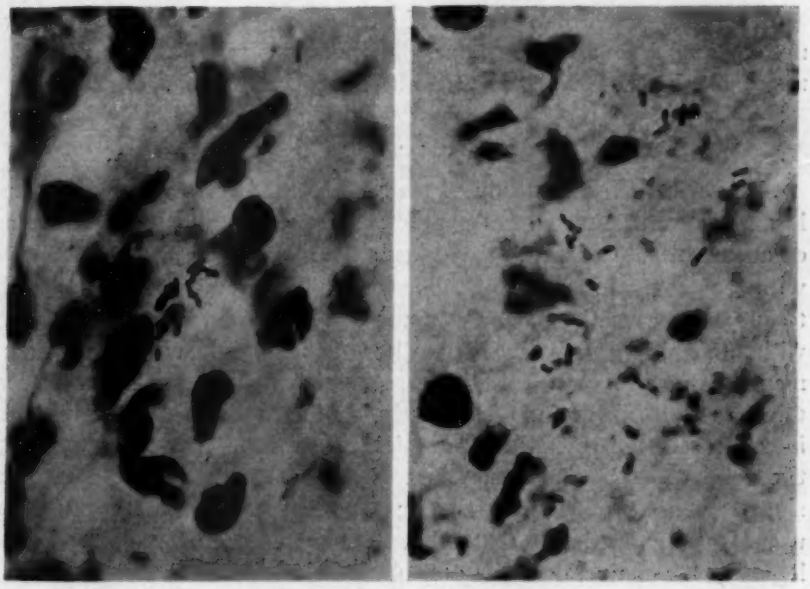

Fig. 6.—Acid-fast bacillary forms in a tuberculoid lesion. Many of the bacteria have a beaded appearance; × 1,350.

reaction progresses along, and peripheral to, the vascular channels until the deeper and less resistant subcutaneous tissues are reached. Here the process is continued, with the smaller vascular channels finally disappearing as a consequence of atrophy from pressure and eventual necrosis of the morbid process. In the meantime many of the monocytic cells assume an epithelioid appearance, and fibrous connective tissue is formed at the outer zone of the proliferating cells. This, in turn, eventually becomes granulomatous, with numerous blood vessels and an infiltration of lymphoid cells. The giant cells of the Langhans type which are often present in considerable numbers in the lesions become evident as a consequence of the fusing of mononuclear cells constituting the

primary cellular reaction. The central portions of the lesions, which are avascular and subjected to the noxious influences of the infective agent, become necrotic and calcification follows.

The pathologic change of the nontuberculoid diseases was a simple pyogenic abscess in which the salient features were a single encapsulated, or several diffuse, areas of necrotic substance surrounded by fairly vascular granulation tissue. Some abscesses contained mineral salts and others did not. Occasionally giant cells were present, but the peripheral monocytic and epithelioid reaction characteristic of tuberculoid lesions was absent. Likewise, acid-fast bacteria could not be demonstrated.

The lesions which were later found to be pyogenic abscesses were not obtained from any one source. These lesions were sent to the laboratory from Idaho, Illinois, New York, Oregon and Utah.

COMMENT

It is evident from a study of material secured from widely separated localities that the structural character of nodules situated in the subcutaneous tissues of cattle that react to tuberculin cannot be correlated with the geographic origin of the lesions. This would lead one strongly to suspect a causative factor common to all. Grossly, the lesions were without significant difference regardless of their origin, although Traum [5] mentioned the involvement of the regional lymphatic structures in certain cases in California. Apparently, so far as the histologic response is concerned, the so-called skin lesion of cattle is essentially the same throughout the United States. It is reasonable to assume that occasionally a nonspecific type of abscess may sometimes be confused at necropsy with the lesion that I have designated as tuberculoid. Histologically, the distinction is not difficult.

In any review of the subcutaneous nodule, the etiology of these structures is usually considered. Although this study was confined, by nature of the material, to the morphologic aspects of the disease, speculations as to the agent responsible for inception of the changes cannot be avoided. Even though Traum, who first reported the condition in the United States in 1916, did not agree that the disease was tuberculous, the condition is considered by many investigators as representing a variety of tuberculosis. The evidence in support of the contention that the lesions are expressions of infection with Mycobacterium tuberculosis can be stated briefly as follows: (1) The histopathologic changes of the lesions are often indistinguishable from those induced by Mycobacterium tuberculosis; (2) acid-fast bacteria, morphologically not essentially unlike those responsible for true tuberculosis, occur in many of the lesions; (3) cattle affected with subcutaneous nodules frequently

5. Traum, J.: Cornell Veterinarian **13**:240, 1923.

react to a diagnostic injection of tuberculin, and (4) cattle with these tubercle-like nodules are often from herds in which genuine tuberculosis has been demonstrated previously.

As impressive as this evidence may be, it is largely presumptive and does not constitute definite proof that Mycobacterium tuberculosis is the provocative agent. On the contrary, formidable arguments can be advanced to support the point of view that the infection is not truly tuberculous. These might be summarized briefly as follows: 1. The histologic aspects of a tubercle-like structure are unreliable criteria as to the nature of the etiologic agent responsible for a given lesion. The so-called tubercle is the result of a nonspecific, cellular reaction. Anatomic units or "tubercles" remarkably similar in cellular detail can be induced experimentally with such markedly dissimilar agents as Mycobacterium tuberculosis, Brucella abortus and silicon dioxide. Therefore, the histologic characteristics of a given lesion are no criteria of its specificity. 2. Attempts to culture from the lesions acid-fast bacteria that will cause tuberculosis in experimental animals have failed, as have attempts to produce tuberculosis by injection into cattle, swine, rabbits, guinea-pigs and chickens of emulsions of tissue prepared from the lesions.[6] 3. A positive reaction to mammalian or avian tuberculin does not indicate an infection with the organism of mammalian or avian tuberculosis respectively. Group reactions may occur in which animals sensitized by infection with the organism of human or bovine tuberculosis may react to avian tuberculin, and conversely, those infected with the organism of avian tuberculosis may react positively to mammalian tuberculin.[7] Sensitization to tuberculin may be due, in these cases, to undescribed and unidentified species of Mycobacterium in the lesions, or to a transitory residence in the animal of the bacilli of avian tuberculosis. 4. The localization of the lesions and the fact that in a large percentage of the affected animals internal lesions of tuberculosis are not discovered are contrary to what might be expected of the organism of true tuberculosis.[7a]

---

6. In two instances I have succeeded in obtaining the organism of avian tuberculosis from subcutaneous lesions of cattle, but I do not believe this organism of significance in the pathogenesis of the condition; too many additional lesions have failed to yield such organisms.

7. Dolgopol, Vera B.: J. Infect. Dis. **49**:216, 1931. Feldman, W. H.: J. Am. Vet. M. A. **83**:344, 1933. Schalk, A. F.: ibid. **72**:852, 1928.

7a. Further evidence attesting to the localized character of the disease was recently brought to my attention by Dr. C. U. Duckworth, of the California Department of Agriculture, Sacramento. In a personal communication, Dr. Duckworth presented evidence showing that sensitivity to tuberculin disappears following the surgical removal of tuberculoid lesions of cattle. The procedure was carried out among approximately 220 animals that were affected with lesions of this character, and when the animals were subsequently retested with tuberculin, they failed to give a positive reaction.

Although it can be stated that information available is definitely against the possibility of the tuberculoid subcutaneous nodule of cattle being due to a tuberculous infection, the final answer to the question of etiology must await additional investigation. The recent work of Daines and Austin,[8] in which a variety of heretofore undescribed acid-fast organisms was isolated from a large number of so-called skin lesions, may be significant. However, until the lesions can be reproduced experimentally more or less consistently by the organisms isolated from the spontaneous lesions, the part of these organisms in the pathogenesis of the lesions cannot be precisely stated.

Some, including Carpenter and Goldberg and Runnells, have made comparative studies of the so-called skin lesions of cattle and those of lupus vulgaris of man in an attempt to recognize a possible relationship between the two conditions. Carpenter and Goldberg considered the two diseases sufficiently alike structurally to conclude that the lesions in cattle "are identical with skin tuberculosis (lupus vulgaris) in man." Runnells also noted a morphologic similarity between the lesions of these two conditions, but pointed out some significant differences in that the lesions of lupus vulgaris are avascular, do not have a perivascular inception and appear to be more progressive.

I have also examined material from cases of lupus vulgaris in man, and although histologically a general resemblance to the subcutaneous lesions of cattle exists, the fallaciousness of drawing conclusions from analogous lesions in different species should be kept in mind. I have shown [9] in experimental tuberculous infections that the character of the reaction of the tissue to a given form of Mycobacterium tuberculosis varies with the species which has the infection. Tuberculosis is a disease of inconsistencies, and proper consideration must be given to many factors before the exact character of a given lesion can be ascertained. Therefore a morphologic comparison of the lesion of lupus vulgaris of human beings with the subcutaneous nodules of cattle for the purpose of determining a possible etiologic relationship is likely to lead to wrong conclusions.

That rarely lesions of the subcutaneous tissues may represent a true tuberculous infection is evident from the reports of Day,[10] Daines and Austin and Nieberle. Daines and Austin in one instance isolated Mycobacterium tuberculosis (bovis) from an animal which had internal lesions as well as cutaneous lesions of tuberculosis.

Nieberle [11] reviewed briefly a case originally described by Joest, in which there were multiple, flat, nodular masses in the subcutaneous tissues of the cervical, thoracic and abdominal regions of a heifer affected

8. Daines, L. L., and Austin, Harold: Am. Rev. Tuberc. **27**:600, 1933.
9. Feldman, W. H.: Arch. Path. **11**:896, 1931.
10. Day, L. E.: J. Am. Vet. M. A. **72**:782, 1928.
11. Nieberle, K.: Ergebn. d. allg. Path. u. path. Anat. **25**:631, 1931.

with generalized tuberculosis. Nieberle also mentioned cases of tuberculosis of cattle in which the cutis was involved, and Besnoit and Robin [12] reported the occurrence of a similar case. The animal in Besnoit and Robin's case was an old cow with tuberculous lesions of the subcutaneous tissue on the right side of the wall of the thorax. At necropsy, generalized tuberculosis was observed, and the subcutaneous involvement was found to represent an extension from a subpleural tuberculous abscess. Lesions of the skin and subcutaneous tissues induced by the organism of bovine tuberculosis must occur rarely, and when present are probably, in the majority of instances, part of a tuberculous process present primarily elsewhere in the body. Such lesions must be assumed to arise by direct extension or as a result of a hematogenous infection. Differing in this regard are the often encountered subcutaneous tuberculoid lesions which are apparently not due to the organism of true tuberculosis and are limited in their distribution to the exterior surfaces of the body.

SUMMARY

A histologic study was made of the spontaneous tuberculoid lesion of the subcutaneous tissues of cattle in which the reaction to tuberculin had been positive and in which lesions of true tuberculosis were not found. The specimens were obtained from twenty-one states of the United States and from Canada. There were thirty-four specimens which were considered tuberculoid because of the resemblance of the histologic characteristics to those of lesions of tuberculosis. Fourteen other specimens disclosed lesions that were considered nonspecific pyogenic abscesses, and two others revealed only thickening of the corium; one was found to represent an adenoma of the sebaceous glands. Acid-fast organisms were present in twenty-two, or approximately 64 per cent, of the thirty-four lesions that were designated as tuberculoid.

No significant differences were observed in the character of the tuberculoid lesions in different sections of the United States, and the one lesion obtained from Canada was similar to the others studied.

CONCLUSIONS

The subcutaneous tuberculoid or so-called "skin lesion" of cattle which react positively to tuberculin appears to be widely distributed over the United States. The literature at this time suggests that the condition occurs rarely in Continental Europe or in the British Isles.

Histologically, the lesion is essentially a monocytic and epithelioid cellular reaction, with a peripheral and granulomatous encapsulation.

Although the lesions usually closely resemble in appearance those of tuberculosis, evidence at this time indicates that agents other than the bacteria of true tuberculosis are probably responsible for the disease.

---

12. Besnoit, C., and Robin, V.: Rev. vét. **5**:409, 1923.

General Review

THE NATURE OF SO-CALLED XANTHOMA

A CRITICAL REVIEW

GERHARD GRUENFELD, M.D.
AND
M. G. SEELIG, M.D.
ST. LOUIS

INTRODUCTION

Certain granulomatous or tumor-like formations encountered in the most diverse parts of the body and under a great variety of clinical conditions are distinguished by a special cell form, the main characteristics of which are a comparatively large body of protoplasm with distinct multiangular borders and a foamy structure, the latter brought about by the removal of numerous droplets of lipoids by the fat-dissolving solutions employed in the routine methods of preparation.

Since such cells were first observed in a peculiar tumor of the skin named "xanthoma" or "xanthelasma" (on account of its yellow or yellowish-brown color), they are called "xanthoma cells" or, more descriptively, "foam cells."

Subsequent observations have established a number of facts which, in their potential correlation, have made the pathology of the xanthoma cell highly interesting. These are: 1. Pathologic structures containing xanthoma cells may occur in many other organs besides the skin. 2. Xanthomatous formations occur as solitary, but also as multiple, sometimes widely distributed tumors. 3. Xanthomas, both single and multiple, are often encountered in patients with an increase of cholesterol in the blood. 4. The droplets that give the xanthoma cell its characteristic appearance consist of lipoids, chiefly cholesterol and its esters.

The occurrence of xanthomatous tissue changes simultaneously with a disturbance of the blood chemistry suggests that these formations are not neoplasms but products of abnormal metabolism. Many authors assume them to be storage tumors produced by the pathologic fixation of superabundant lipoids resorbed from the circulation, and explain their structure more on the lines of a granuloma than on those of a neoplastic cell proliferation. It has been proposed to discard the term "xanthoma"

From the Research Department of the Barnard Free Skin and Cancer Hospital.
This study has been aided by a grant from the Committee of Scientific Research of the American Medical Association.

because these lesions are not true autonomous growths and at best deserve the ending "oma" to express a tissue reaction analogous to that following an injection of paraffin, namely, the so-called paraffinoma. With such philologic criticism we are in accord, and this study has been prompted by the desire for a clearer etiologic understanding of the pathology of the foam cell, which would permit a scientific classification of its various forms.

Rowland, in his meritorious treatise on the anomalies of lipid metabolism, reviewed all detailed knowledge pertaining to this problem and voiced the opinion that all tumors or granulomas containing xanthoma cells are manifestations of one disease, a disturbance of the lipoid metabolism to which he gives the name "xanthomatosis."

Rowland also advocated a monistic conception of the histogenesis of the foam cells. According to him and others, foam cells are always cells of the reticulo-endothelial system, which acquire their shape as the result of their phagocytic reaction to the presence of lipoids (increase in normal lipoids or the presence of foreign lipoids). This contention is not merely of theoretical importance. The surgical pathologist frequently encounters biopsy specimens in which the predominant finding is xanthoma cells, usually in connection with a varying degree of fibrous tissue formation. The question arises whether it is justifiable to diagnose xanthomatosis in the sense of Rowland's conception on the basis of this microscopic finding alone, or whether pathologic formations of different and entirely unrelated genesis can assume the xanthomatous structure. It is evident that if Rowland's theory is applicable to all cases, the problem of xanthomatous formation is settled in very simple fashion and the pathologist is justified in making the microscopic diagnosis of xanthomatosis in every instance of foam cell tumors.

According to recently accumulated observations, the pathology of xanthoma is of very wide scope. Innocuous and rather common lesions like the xanthoma of the eyelid or the so-called giant cell sarcoma of the tendon sheath line up with such formidable systemic disorders as Niemann-Pick's disease and Gaucher's splenomegaly. Rowland's classification may be given in order to illustrate how the chapter on xanthoma has expanded:

A. Essential or primary disturbances of lipid metabolism with characteristic clinical and anatomic expressions
   1. Essential xanthomatosis (the variety affecting the skin, mucous membrane, tendon sheaths or viscera
   2. Niemann-Pick disease
   3. Schüller-Christian disease
   4. Gaucher's disease

B. Symptomatic or secondary forms of lipid metabolism
   Such forms are associated with diabetic lipemia and certain disorders of the liver and kidney in which the metabolic disturbance is secondary

A causal relationship between the formation of xanthomas and the abnormal cholesterol content of the blood is most convincingly demonstrated in certain cases of diabetes. Here, disappearance of the tumors (or granulomas) follows restoration of the blood chemistry to normal conditions. In other forms of xanthomatosis the involvement of the reticulo-endothelial system is most obvious, as in Gaucher's disease, Niemann-Pick's disease and other generalized forms with extensive involvement of the bone marrow.

The monistic conception of xanthomatous granulomas or tumors has strong arguments in its favor, but from our own experience and from a perusal of the literature we have gained the impression that for many cases, especially for solitary tumors, this explanation is without sufficient proof.

It seems to us that the time is ripe for a critical analysis of what we have called the "monistic" or, possibly better, the "unifying" theory of xanthoma formation. As this theory is based on two assumptions, (1) the derivation of the xanthoma cell from the elements of the reticulo-endothelial system and (2) a preceding hypercholesteremia, we shall review the subject under the two heads of pathologic anatomy and pathologic physiology. This separation is advisable because the correctness of one phase of this theory may stand in spite of an apparent weakness of the other.

I. PATHOLOGIC ANATOMY

In his textbook, "Traité des maladies de la peau," published in 1836, Rayer portrayed, under the title "plaques jaunâtres," yellowish skin efflorescences, usually located on the eyelids, but occasionally found in other parts of the integument. Several Englishmen, Addison and Gull, Wilson and W. F. Smith, published the first detailed clinical reports. The last mentioned author used the term "xanthoma," which soon became the accepted term for this lesion. Microscopic examinations were reported by Pavy, Fagge, Hutchinson, Waldeyer, Virchow, Kaposi and Chambard, all of whom are quite in accord in describing the histologic picture. They found a proliferation of the cellular and fibrous elements of the cutis and peculiar large cells loaded with numerous fat droplets. While most of these authors considered the whole process, including the appearance of the cells containing the fat droplets, to be a reaction of the connective tissue, other contemporary students, e. g., Wilson, Hebra[1] and Kaposi, Geber and Simon, interpreted the fatty cells as hypertrophic formations of sebaceous glands to which, indeed, they have a striking resemblance in view of the foamy structure of their protoplasm.

1. Later on Hebra revised his opinion; he regarded xanthoma as a peculiar fatty neoplasm.

Chambard published excellent lithographs of microscopic sections and adopted the name "xanthoma" from W. F. Smith for the pathologic findings, thus introducing this term into the continental literature. Among the great number of older publications on the histology of xanthoma, the ones by Török and Geyer seem to be of special interest. Török found the xanthoma cells arising from the adventitia of small vessels, but, not knowing that their granules differ chemically from the fat in regular adipose tissue, he believed them to be embryonal fat cells. Geyer, on the other hand, brought forth equally good evidence for the origin of these cells from the intima of the smallest lymph vessels.

Toepfer described a xanthoma with absence of foam cells, the fatty granules being contained in the typical spindle cells of hypertrophied connective tissue.

The early investigators also discussed the general pathology of these lesions. Waldeyer (1871) emphasized the difference between a fatty cellular degeneration and the infiltration of cells with fat in his case of xanthelasma palpebrarum: "The fat droplets assume considerably larger size and there is no evidence that these fat inclusions damage the cells, because, after extraction of the fat, a good deal of protoplasm becomes visible, and a well formed nucleus appears. No colliquation of cells or any detritus can be found."

Virchow corroborated Waldeyer's description with the report of a case of molluscum lipomatodes (in his terminology) and a xanthomatous growth of the conjunctiva which had obliterated the cornea. He described a xanthoma nodule as follows: ". . . The peripheral and the young elements consist almost entirely of proliferating connective tissue cells, which occasionally somewhat resemble sarcoma on account of their great number and their size. Nowhere was there any evidence that the progressive infiltration with fat initiated a necrobiotic process. This process may be compared with the fatty metamorphosis of certain connective tissue structures as, for instance, that of the inner lining of the aorta, but the integrity of the cells (in the case of xanthoma) is not interfered with. . . ." This reference to the atheromatous degeneration of the aorta anticipated the establishment, at a much later date, of a chemical relationship between these processes.

Emphasizing the rôle of the peculiar foamy cells in the histologic picture of xanthoma, de Vincentiis and Touton regarded these lesions as neoplasms, inferring that every xanthoma cell is derived directly from another one of the same structure. Unna was very specific about a totally different histogenesis. In a cutaneous xanthomatosis in a diabetic patient, he found fibroblasts in all stages of transition to foam cells. In the center of a xanthoma, surrounding fat crystals, were enlarged epithelioid-like cells stuffed with fat droplets and not infrequently rup-

tured by these enclosures. Toward the periphery, the cells gradually assumed the shape and size of regular fibroblasts while the content of fat droplets decreased conspicuously. A zone of normal spindle cells formed the border of the focus. Krzysztalowicz substantiated these observations and concurred with Unna in his opinion about the fibroblastic origin of the xanthoma cells.

By this time the clinical aspects of xanthomatous lesions had become quite complex. It was known that xanthomatous lesions of the skin were frequently associated with jaundice and diabetes. They were observed as solitary tumors, as symmetrical lesions (i. e., on the eyelids) and as multiple and even generalized growths. Macroscopically, the tumors considered to belong to this group varied greatly in size, site, depth, color and consistency. The question arose whether these different pathologic formations could still be considered to express an entity on the strength of their histologic appearances.

Török found typical foam or xanthoma cells in all the different clinical forms (xanthoma of the eyelids, the single and multiple tumors of the skin and the xanthomatous lesions associated with jaundice). However, he regarded the diabetic form as a separate disease of an inflammatory nature in which an infiltration with exudate cells and a necrosis of fatty degenerated cells prevail.

Unna, on the contrary, considered the diabetic xanthoma typical of and identical with generalized xanthoma. But his comparative studies led him to the conclusion that the solitary xanthomatous tumors containing giant cells should be separated from the groups of generalized xanthoma; that, likewise, xanthoma palpebrarum is a pathologic process *sui generis* because the accumulation of fat takes place extracellularly in the lymph spaces.

If one accepts these somewhat divergent observations of the earlier students as authentic it appears that cutaneous xanthoma shows as much variation in histologic detail as in clinical appearance. There is, however, no histologic formation specific for any one of its clinical forms in spite of repeated attempts to reserve certain microscopic peculiarities for some of them. Any such contention advanced by an author has been disproved by an equally competent observer of clinically identical material. The differences in the microscopic observations are apparently incidental to the individual cases and more dependent on the developmental stage of the lesion than on any etiologic specificity.

More recent observations on a larger series of cases of cutaneous xanthoma support the conclusion that variations in the histologic structure are without significance for an etiologic differentiation.

Additional evidence for a close relationship of all the different clinical and histologic pictures of cutaneous xanthoma was gained when

Stoerck discovered that the characteristic cellular inclusions of the xanthoma cell were not fat but a doubly refractive lipoid substance. Although Stoerck believed that this lipoid was a product of protein decomposition (he called it "protagon"), Pinkus and Pick soon identified it as a cholesterol compound and associated it with the hypercholesteremia kown to exist often in patients suffering from generalized xanthomatosis. The same chemical substance was found in all forms of xanthoma—xanthoma of the eyelids, solitary xanthomatous tumors and the xanthoma cells that sometimes appear in the vicinity of chronic foci of suppuration. The details of the histologic structure came to be considered as of less importance than the presence of the cholesterol compound in the tissue. Lubarsch and Bross studied a case of severe and rapidly fatal diabetes with a yellow discoloration of the total skin surface, believed to be jaundice, in which an autopsy disclosed extensive xanthomatosis (cholesterol ester deposits) in the visceral organs and the bone marrow. Under the microscope, the lipoid droplets were found: (1) as extracellular masses engorging lymph spaces and small vessels; (2) within the endothelial cells of lymphatic and blood capillaries; (3) in typical connective tissue cells and in proliferating spindle cells arranged along the course of blood vessels; (4) in xanthoma cells which appeared to develop from the lining cells of the lymph spaces. The yellow discoloration of the skin was due to a heavy infiltration of the cutaneous lymph spaces with columns and droplets of lipoid substance.[2] Lubarsch concluded that the histologic details of xanthomatous lesions are of only minor importance. The essential pathologic factor is the flooding of the circulation with lipoids and their stagnation in the lymphatic pathways. Incidentally, and possibly owing to mechanical circumstances, endothelial or connective tissue cells may react to the increasing concentration of these substances with the formation of foam cells. Gans, in his recent textbook on the histology of cutaneous diseases, also doubted the significance of histologic differences in the structure of xanthomas. He expressed the opinion that the cells which participate in the formation of xanthoma or foam cells are either endothelial or connective tissue cells, and that the infiltration with fatty acid esters of cholesterol is a phenomenon of storage rather than a degenerative process of the protoplasm, because karyokinesis takes place in young xanthoma cells. In older foci, a replacement of the lipoid-containing cells by dense connective tissue takes place; this replacement may go so far as to obliterate all traces of xanthomatous substance and

2. Diabetic xanthosis has been observed and described by von Noorden and Umber without reference to xanthomatosis and hypercholesteremia. According to recent investigations, the discoloration of the skin is usually due to an excess of lipochromic substances in the blood (Burger and Reinhart).

cells, the only remnant of the previous cholesterol infiltration being a yellow pigment, lipofuscin, in cells reduced to normal dimension and shape.

Pollitzer and Wile, describing the histologic variability of cutaneous xanthomas in one and the same case, claimed that the xanthoma of the eyelids is histologically different from other forms of cutaneous xanthoma. They found that the condition is due to a degeneration of the muscle fibers contained in the eyelids.

Visceral Xanthomatosis.—Visceral xanthomatosis associated with the cutaneous lesions was described by the early English observers. In the more recent literature, Murchison is often cited as having published the first report, although in his paper dealing with a case of jaundice and xanthoma of the eyelids he mentioned only a cirrhotic change in the liver.

Fagge reported the case of a patient who had intensive jaundice of many years' duration, xanthomas of the eyelids and cutaneous tumors on the hands. At autopsy, cirrhosis of the liver was found as the cause of the jaundice. The vocal cords and the mucosa of the trachea [3] were the site of yellow patches with a histologic structure identical with the xanthomatous lesions of the skin. Furthermore, similar patches occurred on the endocardium and on the intima of the large vessels including the pulmonary artery. Xanthomatous tumors were also found arising from the tendon sheaths of the fingers.

Pye-Smith had a patient suffering from intermittent jaundice due to stones in the common bile duct who, at a later stage of the jaundice, showed xanthomatosis that was at first confined to the eyelids and palmar surfaces of the hands. The cutaneous lesions spread slowly, uninfluenced by temporary improvement of the jaundice. She finally succumbed to erysipelas. The autopsy confirmed the diagnosis of stones in the common bile duct. Patches of xanthoma were found on the peritoneal surface of the spleen and in the mucosa of the bile ducts.

In a patient with generalized cutaneous xanthoma, Balzer found patches on the endocardium and pericardium. The cause of death was an extensive pulmonary tuberculosis.

Interesting is the publication of Lehzen and Knauss concerning the occurrence of generalized cutaneous xanthomatosis in two sisters, 11 and 9 years of age. The elder sister died, probably from heart failure. The clinician (Leube) had suggested the possibility of xanthomatous lesions in the heart. At autopsy, this suspicion was confirmed. The mitral valve carried xanthomatous plaques, likewise the intima of the aorta, pulmonary artery and coronary vessels. The left carotid artery was almost completely stenosed by the xanthomatous proliferations, xanthoma cells being present in the walls of the vessels. Multiple xanthoma was also found on tendons and joint capsules of the hands.

Pinkus and Pick reported on pachymeningitis interna xanthomatosa in a patient with hypertrophic cirrhosis of the liver, with jaundice and extensive xanthomatosis of the skin.

Low's case is almost identical with the one described by Lehzen and Knauss.

---

3. Observations on xanthomatosis with a localization in the larynx and trachea were recently published by Finney, Montgomery and New.

Chvostek's publication is especially valuable on account of a detailed histologic study. The autopsy of a jaundiced patient revealed a diffuse proliferation of what appeared to be typical xanthoma cells in the liver. These cells were seen developing from Kupffer's cells and producing a distortion of the hepatic cell columns and biliary capillaries. In the skin of the same patient there existed a rather generalized xanthomatous eruption, which on microscopic examination was found to consist of foam cells. These cells, however, appeared to be transformed fibroblasts, no connection with endothelial cells being demonstrable. Still more remarkable were the histochemical differences in the two types of foam cells in the same patient. The cellular inclusions of the foam cells in the cutaneous lesions were doubly refractive in polarized light and stained with lipoidophil stains; these reactions could not be reproduced in the foam cells of the liver. Chvostek considered it possible that unknown chemical reactions in the liver interfered with the typical reactivity of the lipoids. Indeed, the histochemical methods for the detection of the so-called lipoids are based on such very complex and incompletely understood reactions as to make the evaluation and interpretation of sections so processed rather difficult (Arndt). Chvostek's case also suggests that hypertrophic biliary cirrhosis might be produced by a xanthomatous proliferation of the endothelial cells of the liver. Similar processes might have been responsible for some of the other cases of xanthomatosis associated with biliary cirrhosis and jaundice, this histologic process often having been obscured by the fibrous end-stage. Hardaway and Hallopeau independently advanced the theory that localizations of xanthoma in the liver and pancreas, respectively, produce the jaundice and the diabetes so frequently found associated with xanthomatous conditions of the skin. Of course, these hypotheses cannot be regarded as a generally valid theory. Sickemeier described a case of cutaneous xanthomatosis with cirrhosis of the liver and jaundice, in which the process in the liver was due to a miliary hepatic tuberculosis. Schulte, also, reported a case of visceral xanthomatosis, characterized by severe jaundice of long duration, due to an obstruction of the common bile duct by a carcinoma of the pancreas. Foam cell proliferations were found in the capsule of the liver and spleen and in a solitary xanthomatous tumor of the skin in the bend of the elbow.

Lubarsch's case (see also Bross), referred to before, also represents typical visceral xanthomatosis.

We have reviewed these reports somewhat in detail, because they show convincingly not only that xanthomatous cell proliferations may occur in internal organs, but also that the cutaneous and visceral lesions are etiologically related. This does not obviate certain histologic and sometimes even histochemical differences in the various manifestations in one and the same case.

Xanthomatosis of the Hematopoietic Organs.—Quite recently these pathologic conditions have become the object of numerous investigations. Unlike the clinical forms enumerated in the foregoing section, this group of xanthomatous diseases shows a lesser tendency to be manifested in lesions of the skin. This fact may explain why clinical recognition has been achieved only in recent years. Indeed, in many instances the xanthomatous cell proliferation is restricted to the organs of the hematopoietic system.[4]

A diabetic metabolism occasionally may here, as in other forms of xanthomatosis, account for the development of the lesions. Representative of such a secondary xanthomatosis in the hematopoietic organs is the so-called diabetic lipoid hyperplasia of the spleen. (The literature has been reviewed by Pick.) This condition develops occasionally in patients who succumb to a severe, rapidly progressing diabetes, with lipemia and hypercholesteremia. The typical pathologic changes consist in a replacement of the splenic pulp by foam cells containing droplets of cholesterol esters. In a few cases the same changes have been found simultaneously in the bone marrow, in visceral lymph nodes and in the liver. In cases in which the xanthomatous process involved also the intima of large vessels and the endocardium, the pathologic picture approached that of a type of generalized diabetic xanthomatosis described by Lubarsch and Bross.

The xanthomatosis of hematopoietic organs *without* underlying diabetic diathesis is, in the light of present day knowledge, not an entity but a group of several interesting diseases distinguished from one another by clinical and chemical peculiarities. Three typical forms are recognized: (1) Gaucher's disease; (2) the Hand-Christian-Schüller syndrome, and (3) Niemann-Pick's disease (Rowland; Chiari; Chester; Henschen).

The histology of Gaucher's disease differs noticeably from that of the other forms, because the large pale cells found in this condition have not the foamy protoplasmic structure of xanthoma cells. However, it is included in this group for the reason that these cells are of the same derivation as the foam cells and also contain a lipoid substance.

The Hand-Christian-Schüller syndrome is produced by xanthomatous changes of the bone marrow of the skull. By the pressure exerted on the adjacent organs the symptoms of exophthalmos, diabetes insipidus and possibly other pituitary dysfunctions arise. The xanthomatous proliferations sometimes involute spontaneously and, according to Sosman and Lazarewa, are sometimes radiosensitive. Abrikossoff and

4. Peripheral lymph nodes which might present themselves for biopsy are rarely involved. The case reported by Robertson and Warren seems to be exceptional in this respect.

Herzenberg (1929), Herzenberg (1928), Pick and Lubarsch have discussed the question whether cases without the typical distribution of foci in the cranial bone marrow, as described by the original observers, may justly be included in this group. Chiari and Davison have made a special study of xanthomatous lesions in the brain in this disease. The pituitary disturbances are frequently the result of a xanthomatous involvement of the nerve or glandular tissue and not always due to pressure from adjacent xanthomatous lesions of the bone. Occasionally, xanthomatous (foam cell) foci can be found widely distributed throughout the central nervous system.

Niemann-Pick's disease is considered to be a racial and familial disease occurring in female infants of Jewish extraction. It usually terminates fatally before the patient reaches the second year of age. Xanthomatous proliferations are found mainly in the spleen and liver, but may involve almost any organ—bone marrow, lymph glands, lungs and brain.[5]

The literature on these diseases is almost contemporary and is still increasing at a fast rate. Adequate surveys have been made repeatedly (Pick; Rowland), and so it may suffice to point out certain histologic details. All three diseases are characterized by the proliferation of large pale cells, the histology of which shows certain special features. The Gaucher cell does not assume the honeycombed or foamy appearance, because the specific lipoid substance, kerasin (Epstein), does not dissolve in fat solvents as do the lipoids in other xanthoma cells, nor does it give color reactions with fat stains or double refraction in polarized light. Certain fibrillar structures can be produced in its protoplasm with special staining methods, which help to identify the cell. Gaucher cells develop in the spleen from reticulum cells, while the endothelium of the venous sinus remains at rest. A second source of the Gaucher cells is often the periadventitial cells of the splenic arterioles. Gaucher cells may vary in size and shape considerably more than other xanthoma cells. They may be found also in the liver and bone marrow; in a few cases the latter has been found to be predominatingly involved.

The foam cells found in Hand-Christian-Schüller's disease are of typical shape and contain droplets of cholesterol and its fatty acid esters. According to Pick, they originate from reticulum and periadventitial cells exclusively. A slowly fibrosing granulation tissue supervenes and replaces the foam cells in a later stage of the process. This granulation tissue is entirely absent in the histologic picture of Gaucher's disease and Niemann-Pick's disease, in which fibrosis occurs, too, but is brought about by a direct condensation of intercellular substance.

5. Pick and Bielschowsky believe that congenital amaurotic idiocy, type Tay-Sachs, is a lipoidosis with identical histology distinguished from Niemann-Pick's disease by the predominantly cerebral localization (Pick).

The foam cells found in Niemann-Pick's splenohepatomegaly have also the appearance of typical xanthoma cells. Their cellular inclusions react positively to lipoid stains, although with a different shade of color. Chemically, they have been identified as phosphatid lipoids or lecithin. The pathologic process is far more generalized than might be suspected from the appearance in the gross. In addition to the spleen and liver, the visceral lymph glands, bone marrow, lungs, thyroid gland, salivary glands, the connective tissue in general, the muscle tissue (especially that of the heart) and frequently the central nervous system show phosphatid substances deposited either in regular tissue or in foam cells. The foam cells develop mostly from reticulum cells and to a lesser degree from the endothelial lining of small vessels. However, commensurate with the diffuseness of the process, other cell types undergo foamy transformation—liver cells, the cells of the pulmonary alveolae, fibroblasts, glandular epithelium, muscle and nerve cells.

These three diseases form the group of primary xanthomatosis of the hematopoietic system. Each disease is clinically, histologically and chemically sufficiently different for one to ascribe autonomy to each of them. Considerable variations in the clinical course and the anatomic distribution may be found in the individual cases, making an even approximately complete description of all known varieties and possibilities an extensive study. Evidently the study of these diseases has furnished much support to the theory that foam cells in general are cells of the reticulo-endothelial system in a stage of reaction to lipoid substances. On considerably less convincing evidence, the observations on cutaneous and visceral xanthomatosis may still be considered compatible with this conception.

The validity of this theory appears to be less well established in the groups of lesions which we shall now take up, even though it is difficult to doubt their systemic nature.

Xanthomatosis of Tendons and Paratendinous Tissue.—The case of Fagge, Lehzen and Knauss, Low, and Hardaway, already cited, show that tumors involving the tendons and paratendinous tissue are one of the potential manifestations of xanthomatosis. Reports of similar cases have been repeatedly published:

Poensgen observed two young boys, cousins, with numerous xanthomas of the skin, tendons and paratendinous tissue without underlying diabetes or icterus.

Carry reported a similar case occurring in a 10 year old girl in whom, in addition to xanthomatous efflorescences of the skin, subcutaneous tumors of the same type arose from the tendo achillis, the patellar ligament and the periosteum of the malleoli. In 1889, Ehrmann (Török) reported on the brother of one of Poensgen's patients, afflicted with xanthomatous tumors of a similar distribution and a probable visceral involvement as suggested by the development of ascites and the enlargement of abdominal veins.

Addison and Gull, pioneer investigators of xanthomatosis, mentioned as early as 1851 the involvement of tendons of the fingers in one of their first three cases. Török's collective paper, published in 1893, refers to seventy cases of xanthoma in ten of which tendinous and paratendinous tumors were mentioned. The series of comparable cases was continued in 1910 by Arning with a report of familial xanthomatosis afflicting a mother and four of her nine children. Other contributions have been made by Hoessli, Knowles and Fischer, Wolodin, Chalatow, Krogius, Harbitz, McWorther and Weeks, and Weidman and Freeman. Chalatow found the xanthoma cells developing from connective tissue cells (cited by von Albertini). Reports have been published more recently by Kusnetzowsky, Krecke, von Albertini, Ollerenshaw, and Nathan and Herrmann.

Tendons and tendon sheaths evidently become rather frequently involved by xanthomatous tissue changes. The intimate relation between these multiple tendon tumors and other forms of xanthomatosis is evidenced by many clinical features in the individual cases. Why a systemic xanthomatosis may manifest itself in these structures, however, can hardly be explained by the theory that it represents a reaction of reticulo-endothelial cells. Aschoff and Landau's definition of this cell system does not include any cell complexes located in these tissues. While we admit the systemic nature of this type of tendinous xanthomatosis, we shall presently refer to a group of xanthomatous lesions of identical anatomic location in which the diathetic character of the xanthomatous process is debatable.

Solitary Xanthomatous Giant Cell Tumor.—Arising in the same tissues, from tendons, paratendinous tissue, aponeurosis or other dense connective tissues solitary tumors have been described by Chaissagnac (1852), Spencer-Wells (1857) and later by Billroth and Czerny (1869) and subsequently in literature quite remote from the sphere of interest of the students of xanthoma (for the literature, see von Albertini).

This solitary, well encapsulated and, in most cases, definitely lobulated tumor is found usually on the hand or the foot in intimate connection with a tendon but rarely involving it. The histologic structure resembles that of a sarcoma of the epulis type, the constituent cells representing several types of mesenchymal cells. It contains spindle or round cells, giant cells, connective tissue fibers and, as a rule, a brown pigment, hemosiderin. Reverdin emphasized the benign clinical course. Heurteaux described the giant cells as being identical with the myeloplax cells of the bone marrow, and Dor found xanthoma cells in this tumor. Dor therefore contended that tumors of this type, heretofore called *myelomes des gaines tendineuses* by the French and *xanthosarcoma giganto cellulare pigmentosum* by the Germans, belong to the category of xanthoma. Pathologists still have not come to an agreement on this question. In connection with our problem, the uniform genesis of foam cell tumors, this controversy is of definite importance.

At present two opinions concerning their nature are generally voiced: (1) These tumors are benign neoplasms of the connective tissue with a more or less incidental admixture of xanthoma cells, these cells being rather unessential or even inconstant elements of the new growth (Spiess; Landois and Reid; Katsurashima; Krogius; von Albertini). (2) These tumors are granulomas following traumas of the tissues or arising from humoral disturbances or caused by both (Fleissig; Weil; Seyler; Sprenger).

After comparing the more recent descriptions, and after studying our own cases, we have the impression that in their microscopic details they do not differ essentially from other xanthomatous formations. The proliferation of fibroblasts, the giant cells, the hemosiderin pigment and the occasional infiltration by inflammatory cells are also found in lesions the non-neoplastic nature of which is well established. Thus the histologic analysis does not contribute much toward the solution of the question as to whether these tumors are neoplastic or identical with xanthomas in general. Von Albertini and Tramonto and Fittipaldi wished to include these tumors in the general category of mesenchymal giant cell neoplasms, more commonly found arising from periosteum, bones, joints, tendon sheaths and skin. They supposedly form an intermediate group between the fibromas and the sarcomas, and develop from embryonic mesenchymal rests. Xanthomatous features are as a rule found only in those tumors which are located at the tendons or in the skin. This is presumably due to chemical peculiarities of these tissues, which is also suggested by the predilection with which general xanthomatosis manifests itself in the same tissues. We have to refer to von Albertini's excellent presentation of this subject containing an extensive discussion of respective cases.

There are certainly features which suggest that these formations are true neoplasms. For instance, their well encapsulated and lobulated form is repeated by other tumors occurring in the same tissues, like chondromas and myxomas. In a considerable proportion of the giant cell tumors of these structures xanthoma cells have been found present only in small numbers or even totally absent (Coenen; Landois and Reid). A few of these tumors have shown tendencies to infiltrate, with erosion of joints and bones. Tumors of the bone marrow similarly composed and apparently related to the so-called osteitis fibrosa cystica of von Recklinghausen [6] have been repeatedly found to contain foam cells (Kolodny; Krogius; von Albertini; Saralegui and Gonzales; Schröder; Lazarewa; Zeyland and Dega).

6. Curiously enough, osteitis fibrosa cystica presents similar problems for an intelligent classification. The histologic and radiologic features characteristic of this condition are found in a localized and in a multiple bone disease. For the latter, in quite a number of cases, a hormonal-metabolic disturbance could be found as conducive to the osteitic changes (Mandl and others).

Investigators who approached the subject from the field of generalized xanthoma also have often proposed a dualistic classification of xanthomas. For instance, Unna separated xanthomatous tumors containing giant cells from the group of ordinary xanthomas, and Pinkus and Pick, who contributed so much to the theory of cholesterol diathesis, also believed that some of the xanthomas are neoplasms with a secondary admixture of xanthoma cells (see later paragraphs). Aschoff's school sponsors a classification of xanthomas which distinguishes between primary xanthomas, or tumors due to a hematogenous cholesterosis, and secondary xanthomas, or degenerative processes in tumors or inflammatory processes (Kammer).

Xanthomatous Formations the Structure of Which Is Predominantly Neoplastic.—In the following a survey is given of xanthomatous formations with a histologic structure dissimlar from that of typical xanthoma inasmuch as the cellular elements predominant in them characterize them as neoplasms.

Endotheliomas: The authority of Pick is again invoked for a number of cases reported by C. H. Smith:

Case 1. Tumor of the tongue with foam cells forming syncytia encroaching on normal-appearing muscle fibers.

Case 2. Tumor of similar composition removed from the labium majus pudendi.

Case 3. Foam cell tumor of the parotid gland.

Case 4. Psammoma of the dura, with xanthoma cells distributed among the spindle cells.

Pick and C. H. Smith interpreted these tumors as interfascicular lymphangioendotheliomas with storage of cholesterol and subsequent transformation of their cells into foam cells, the storing being due to an abnormal metabolism of the tumor cells. A similar storage occurs in certain other tumors, which accumulate glycogen, although the parent tissue lacks this faculty.

Two cases of cystic lymphangioma, identical in their clinical aspects, are described by Kirch. In both instances, the tumor was removed from the subcutaneous tissue in the region of the knee. The cystic cavities contained cholesterol crystals suspended in a thin fluid. The walls of these cysts had the multicolored appearance of xanthofibrosarcoma (solitary xanthoma). Microscopically, the tumors were composed of two different elements: The first was endothelial cells in solid aggregates or forming cysts of greatly varying size. These cells contained hemosiderin and lipoid droplets and were found in all stages of transition toward large xanthoma cells. The second structural element was a sarcomatous stroma of the epulis type entirely free from demonstrable cholesterol infiltration and its cells showed no connections with the foam cells.

A third case of Kirch's was that of an endothelioma of the dura, the neoplastic character of which was especially ascertained by the occurrence of cells of the neurinoma type.

Beitzke found foam cells containing cholesterol esters in a tumor of the cerebellopontile angle of the ganglioneuroma type.

Lipomas and Fatty Tissue: Ewing mentioned the more or less frequent occurrence of lipoid-containing foam cells in lipomas of varying degrees of cell differentiation. More frequently similar appearing polyhedral cells are found which contain droplets of neutral fat and are arranged along the large vessels traversing the tumor.

Adair, Pack and Farrior described a tumor, 13 pounds (5.8 Kg.) in weight, removed from the anterior aspect of the thigh. According to the microscopic examination, this growth was a xanthomyxolipoma with foam cells predominant. A year later a recurrence showed the more uniform structure of liposarcoma. No information is given about the chemical nature of the intracellular droplets.

Proescher and Meredith described as multiple myxocholestolipoma tumors occurring in a woman 32 years of age. Three of them were located subcutaneously and two intra-abdominally in the retroperitoneal space at the insertion of the mesocolon transversum and descendens, respectively. One of the abdominal tumors was removed, but a year after the operation the patient succumbed to a recurrence, with dissemination of tumor masses over the peritoneal surfaces, accompanied by ascites. These tumors consisted of myxomatous tissue with islands of foam cells giving the histochemical reactions of lipoids and showing double refraction in polarized light.

Xanthomatous transformation of the mesentery is rare although typical enough to be the subject of several publications. The xanthomatous changes take place mainly in the areolar tissue of the radix mesenterii (Schlagenhaufer; Versé; Hirsch; Karoliny; Petri). Versé found in most of his cases a blocking of the lymphatic vessels due to tuberculosis, tumor of the liver or carcinomatosis of the thoracic duct or to other mechanical factors. Karoliny observed ten cases of mesenteric xanthomatosis, most of them occurring in elderly and overnourished patients. He considered the mechanical explanation advanced by Versé as not adequate, because he failed to reproduce experimentally xanthomatous changes in the mesentery by compressing or ligating the thoracic duct. Nevertheless, he confirmed Versé's and Hirsch's observation that the lymph nodes in the vicinity of the xanthomatous changes are regularly fibrosed. Petri refrained from offering an etiologic explanation of her case, which was that of a diabetic patient, 69 years old, who died from a far advanced carcinoma of the vulva.

Epithelial Tumors: Corten described a tumor, the size of a fist, removed from the subcutaneous tissue of the buttocks. The microscopic examination showed a stroma and a parenchyma in clear differentiation. The latter consisted of foam cells which in the larger aggregates formed pearl-like bodies giving a modified keratin reaction. The stroma consisted of a tissue of the type of giant cell sarcoma with myeloplax and foamy giant cells (Touton cells). The occurrence of the pearl-like bodies surrounded by foam cells suggested an epithelial derivation of these cells, and the tumor was assumed to have arisen from the misplaced anlage of a sebaceous gland.

Kneringer and Priesel examined a thymoma occurring in an elderly patient. Both the epithelial and the lymphatic elements were in a stage of neoplastic proliferation. Foamy protoplasmic structures were found in cells of both types. The thymus during its physiologic activity is one of the organs that contain greater amounts of cholesterol (Dietrich and Kleeberg). Possibly the chemical affinity of the parent tissue was responsible for the lipoidophil behavior of the tumor cells.

This explanation was also suggested by Corten for the foam cells of a metastatic growth in a suprarenal gland secondary to a carcinoma of the breast. Here the cancer cells contained more and larger droplets of cholesterol esters than the surrounding suprarenal cells. The primary tumor and the metastases in other organs lacked the lipoid infiltration.

Kinoshita found foam cell structure and lipoid infiltration in the cells of a carcinoma of the prostatic gland of otherwise typical appearance. Lipoids are not uncommonly found in high concentrations in normal prostatic glands.

Petri found that the cells in an adenocarcinoma of the stomach and its metastases in the liver assumed the appearance of typical foam cells. Examination in polarized light and differential staining with lipoidophil dyes, however, proved that the cellular inclusions were neutral fats and not cholesterol compounds. In accord with Pick's opinion, referred to before, this fat infiltration was interpreted as due to a peculiarity in the cell metabolism of this special neoplasm.

Foam cell structures in tumors of epithelial or mesothelial derivation are found, furthermore, in certain types of so-called hypernephromas. According to Ewing, certain hypernephroid tumors of the kidneys, which really develop from suprarenal rests, may be composed of lipoid-containing foam cells. Metastatic growths from these tumors wrongly, but not uncommonly, impress the clinician as primary lesions. If such a metastasis occurs in an organ in which other xanthomatous changes are within the scope of the possible, the correct interpretation of a biopsy specimen becomes of utmost importance.

Xanthoma Cells Occurring in the Vicinity of Inflammatory and Neoplastic Processes.—Not infrequently typical lipoid-containing foam cells are found in the walls of salpingitic abscesses (Pick), in the granulomas of leprosy and actinomycosis, in scars, in keloids, etc. Their formation is usually explained as a storage of lipoids in certain groups of connective tissue and blood cells (histiocytes) after cell deterioration has led to a local accumulation of these substances.

Dubs saw xanthoma cells developing from connective tissue cells in two cases of adenocarcinoma of the uterine body. There was neither tissue necrosis nor hypercholesteremia to explain the passive infiltrative lipoid accumulation in the cells.

Xanthoma Cells in the Mammary Gland.—Xanthoma cells have been found in this organ with comparative frequency and in connection with various pathologic changes. Lobeck, in one hundred and sixteen amputated breasts, found areas of xanthomatosis nineteen times. The underlying pathologic changes included acute mastitis, benign tumors, malignant tumors and cystic disease. Careful microscopic and histochemical examination showed that foam cells may be formed either by connective tissue cells and adventitial cells of the blood vessels or by glandular epithelium and carcinoma cells. According to Lobeck, xanthomatous changes in the stroma are always indicative of a coexisting hypercholesteremia, while epithelial or cancerous formation of foam cells may occur without such metabolic abnormality. Hagensen classified the various findings of xanthoma cells in diseased breasts in three groups: (1) Primary xanthoma. Here he reported two observations of his own. The tumors were radiosensitive, amputation of the breast being carried out after marked clinical improvement. A third case was that of Cheatle, which Hagensen mentioned without giving details. A fourth case was that of a xanthomatous nodule at the site of a previous amputation of the breast for carcinoma. At the time of the biopsy, an enlargement of the lymph glands in the supraclavicular region was present, and radiologic observations in the skeleton made the diagnosis of generalized metastases rather certain. (2) Secondary xanthomatous degeneration in fibro-adenomas and carcinomas. (3) Xanthoma cells in traumatic fat necrosis of the breast.

Miller described a large and apparently benign tumor with numerous xanthoma cells in the connective tissue which he classified as cystosarcoma phylloides.

Xanthoma of the Retroperitoneal and Mediastinal Spaces.—Dietrich described a huge giant cell sarcoma originating in the vicinity of the suprarenal gland and infiltrating this organ and the adjacent kidney. Large numbers of lipoid droplets were contained in spindle cells and in characteristic xanthoma cells. Malignancy was suggested by seemingly metastatic tumors of identical histologic structure in the orbits producing exophthalmos, at the base of the skull, in the peritoneum and in the myocardium. There is no reference to the blood cholesterol. Chiari properly suggested that this case might have been one of general xanthomatosis belonging in the category of the Hand-Schüller-Christian syndrome. A similar case reported by Nöthen was that of a tumor of the same localization and histologic appearance. The smaller tumors in the lungs, peritoneum and lymph nodes had a distribution somewhat more in line with a metastatic spread than those in Dietrich's case. Wessen removed an extraretropleural tumor growing with a broad pedicle from an intercostal space, which had a histologic structure of

the type seen in xanthomatous giant cell sarcoma. Heuer removed a xanthomatous tumor, well encapsulated and somewhat larger than a golf ball, from the posterior mediastinum. The point of origin from the thoracic wall could not be determined.

We pause here to summarize this complex, if not confusing, mass of pathologic data as follows:

1. In many cases, solitary xanthoma appears to be a special form of giant cell tumor.

2. Xanthoma cells may be found in neoplasms of epithelial and mesodermal genesis and in inflammatory cell infiltrations and proliferations.

3. The various clinical forms of multiple and generalized xanthoma are interrelated. The histologic pictures show little if any variation, and the occurrence of intermediary cases proves that the factor of localization in certain organs and systems cannot serve as a criterion for a scientific classification.

4. The survey of the pathologic anatomy does not lend support to the contention that multiple or generalized xanthoma can be etiologically explained as a phenomenon of reticulo-endothelial storage in the sense of a phagocytic accumulation of unphysiologic substances withdrawn from the blood stream. Two findings are not compatible with this theory: (*a*) the xanthomatosis of the tendons and tendon sheaths; (*b*) the extreme variability of the localization of xanthomatous changes. The phagocytosis of the reticulo-endothelial system is a physiologic function of normal cells. As shown by the experiments with vital staining, these cells respond to the introduction of foreign substances into the circulation in a typical and predictable way. If xanthomatous cell proliferations developed in a similar way, the great variation in the localization of xanthoma which accounts for so much of the complexity of the clinical aspects of this disease would remain unexplained.

II. PATHOLOGIC PHYSIOLOGY

A humoral basis on which to rest the cellular changes found in xanthoma suggested itself to the first clinical observers of this disease. Addison and Gull, Fagge, and Pye-Smith remarked on the frequent association of xanthomatosis with jaundice. Gilbert and Lereboullet (quoted by Bross) committed themselves to the theory that cholemia produces xanthoma. To Quinquaud belongs the credit of having discovered the first essential facts of the blood chemistry in xanthomatosis. He found the fat content of the blood serum considerably increased in three patients and, according to Chambard, who collaborated with him in this investigation, recognized also an increase of the blood cholesterol. On the basis of these findings, Quinquaud explained the development

of xanthomas as inflammatory tissue reactions provoked by depositions of excess fatty substances in the circulation, the inflammatory tissue proliferation being modified by a reduced oxygen-combining power of the lipemic blood.

For a time disregarded by investigators like Török, Hallopeau and Hardaway, the significance of Quinquaud's studies was reestablished when Pinkus and Pick and Chauffard, Laroche and Grigaut pointed out the occurrence of excessive amounts of cholesterol compounds in foam cells and in the blood serum of patients with xanthoma. The etiologic relation between cholesteremia and xanthomatosis had now become the main issue of investigation. Unfortunately for a further advance in the search for a well established etiology, the blood chemistry in individual cases does not uniformly fit into any axiomatic scheme of a hypercholesteremia-xanthomatosis relationship. It is only fair to eliminate the cases of solitary xanthoma as proof for or against such a relationship, because not a few investigators regard these solitary neoplasms as essential tumors undergoing localized xanthomatous degeneration. Indeed, in the majority of instances of solitary xanthoma the cholesterol content of the blood seems to have been found within physiologic limits, although Weil reported high blood cholesterol also for these cases.

The difficulty in the way of establishing the hypercholesteremia theory arises from the inconsistency of the blood cholesterol findings in cases of generalized xanthoma. On the affirmative side may be listed the xanthomatoses complicating diabetes, icterus and, rarely, lipoid nephrosis. In these cases, without exception, high figures for blood cholesterol have been regularly reported. Furthermore, as a therapeutic test of this theory, involution of the xanthomas can unvaryingly be observed if successful antidiabetic treatment abolishes the concomitant lipemia and hypercholesteremia (Engman and Weiss; Major). Gaal could parallel these therapeutic results in a patient with multiple subcutaneous, tendinous and para-articular xanthomas and an "essential" hypercholesteremia by eliminating lipoids from the diet for a long time.

In the so-called essential xanthomatosis of the skin (xanthoma multiplex), a condition clinically quite similar to the icteric and diabetic xanthomatosis, reports of high blood cholesterol (for instance, by Mook and Weiss and Schmidt) are offset by an increasing number of reports of normal and subnormal levels of cholesterol (Rosenbloom; Rosenthal and Braunisch; Arzt; Siemens; Herrmann and Nathan; Greenbaum; Weidman; Baar; Wile, Eckstein and Curtis). In the Hand-Schüller-Christian syndrome an absence of increase in cholesterol has been observed in some cases (Rowland; Chester), although high values are

usually found during the more active stages of the disease. In Gaucher's disease no known changes occur in the chemistry of the blood. In Niemann-Pick's disease the blood cholesterol is often found increased, although the lipoid infiltration of the cells supposedly consists of phosphatid lipoids and not of cholesterol.

The frequency with which excessive concentrations of cholesterol in the blood are associated with xanthomatous deposits might serve as a crucial test of the hypercholesteremia theory. Such a comparison reveals a marked discrepancy between the frequency of hypercholesteremia and the development of xanthoma. Despite the fact that blood cholesterol reaches probably its highest concentrations in cases of obstructive jaundice (Wells; Leupold) xanthoma develops only in very few patients so afflicted. Diabetic patients with lipemia and hypercholesteremia, after all, do not show a high incidence of xanthoma. Excessive increases in cholesterol appear physiologically during the later months of pregnancy. Chauffard, Laroche and Grigaut found hypercholesteremia in 58 per cent of cases during the first seven months and in 94 per cent during the eighth and ninth month. This increase amounted in the average to 68 per cent, and occasionally surpassed 100 per cent; yet xanthoma is not common during pregnancy.

Westphal, who attributed to cholesterol an important rôle in the pathogenesis of essential arterial hypertension, stated that he found hypercholesteremia in more than seventy of one hundred patients, without making any reference to the existence of xanthoma. According to Joel, persons with a persistent and constitutional hypercholesteremia may remain free from symptoms and demonstrable pathologic manifestations for an indefinite length of time.

As a result of all this, many authors have either denied the etiologic importance of hypercholesteremia or qualified the theory with subtle physicochemical details. While it might be considered rather futile to dwell on the divergence of mere opinions, a brief résumé of these speculations may help to outline the field of further investigation.

Chvostek formulated his opinion as follows: "The essential factor for the infiltration of cells with lipoids is not a cholesteremia but a 'deconstitution' of the cells. A cholesteremia, if present, will only facilitate this process." The "deconstitution" of the cells he believed to be produced by sympathetic or hormonal stimuli. Rosenthal and Braunisch voiced the similar opinion that unknown changes in the chemism of the cells create an affinity for cholesterol, which is deposited intracellularly as ester compounds. Abrikossoff and Herzenberg, subscribing to the same theory, explained the frequent occurrence of hypercholesteremia in cases of xanthomatosis by a concomitant damage of the liver, which fails to eliminate cholesterol at the proper rate. Wile, Eckstein and

Curtis, on the basis of painstaking chemical analysis of blood and tissues, denied that cholesterol either in the blood or in the xanthomatous deposits plays the sole etiologic rôle and contended that a disturbance of the *cellular* fat metabolism more complicated and of unknown nature is at play.

While these interpretations emphasize deviations from the normal functions of cells as primary factors in the pathogenesis of xanthoma, other opinions still maintain that the morphologic changes are representative of the phenomena of storage, the foam and other cell proliferations being only automatic sequels of the unphysiologic concentration of cholesterol in the blood stream.

It can hardly be contended that the negative findings in regard to cholesterol rest on a failure to recognize that the concentration of cholesterol in the blood may vary during the course of the disease. Rosenbloom and Rosenthal and Braunisch made analyses of the blood during the acutely progressive stage in cases of cutaneous xanthomatosis, i. e., at a time when additional tumors were erupting, and they found normal and subnormal values for cholesterol even at this time, when one might reasonably expect changes in the blood to be most marked.

In order to account for the negative results of analysis of the blood in so many cases, and for the irregularity with which xanthoma develops in the presence of hypercholesteremia, a number of auxiliary hypotheses have been introduced. Herrmann and Nathan, following a suggestion of Handowsky, attempted to differentiate between serum cholesterol which can be directly extracted with ether and cholesterol that will go into solution only after protective serum colloids have been destroyed with potassium hydroxide. Assuming that an increase of the unprotected fraction without an increase of the total amount of cholesterol might explain the phagocytic storage in foam cells, they examined the serum of a patient with cutaneous xanthomatosis and normal total cholesterol in the blood. The results of this examination, however, did not lend support to the idea regarding extractable and nonextractable cholesterol.

Schaaf and Werner also expressed the belief that the merely quantitative increase of total lipoids is of minor importance in comparison with the altered quantitative relation of the various lipoid fractions to one another. Therefore they examined not only for cholesterol, but also for cholesterol esters, phosphatids, lecithin and neural fats. They found an increase of total cholesterol in only one of eight patients, but abnormal proportionality between the different lipoid and fat constituents of the serum in all of them. This they believe furnishes an explanation of the development of xanthoma in all those cases in which the quantitative determination of cholesterol and cholesterol esters alone gives no evi-

dence of a disturbed lipoid metabolism. The changed quantitative relations between the different fractions of the serum lipoid supposedly lead to diminished emulsification, because they influence one another in their physicochemical behavior. The changed magnitude of dispersion units provokes phagocytic reactions of certain tissue cells.

Weidman suggested that the present chemical methods of analyzing blood and tissue probably do not succeed in discovering the chemical basis of xanthomatosis. The lipoid substances that one finds at present in blood and tissue may only accompany the chemical agent. Weidman referred to the evolution of the knowledge of ergosterol and vitamin D, which could be isolated only in minute quantities from cholesterol and other lipoids with which they always appear together. However hypothetical this comparison may be, it is true that both the histochemical findings in xanthoma and the blood chemistry in hypercholesteremia are more complex than the emphasis on cholesterol suggests. In the tissues, lipochrome and hemosiderin pigments can be found in most of the instances; sometimes the foam cells store lipoid substances other than cholesterol esters, as in Niemann-Pick's disease and Gaucher's disease. Neutral fat has been found by Fahr and Chvostek. The blood changes, on the other hand, involve the other lipoid fractions, too, because in every case of hypercholesteremia an increase of the neutral fat in the blood serum and often of other lipoids can be found. From all these facts Weidman's suggestion gains support that from the complex mixture of so-called lipoid substances participating in the pathologic changes only few fractions are known and many more may still remain to be discovered.

While the research into the nature of xanthomatosis still falls short of furnishing enough accurate data on which to evaluate properly the rôle of hypercholesteremia, Schönheimer has recently tried to determine how the accumulation of cholesterol in the blood plasma is brought about. He based his examinations on the following considerations: Cholesterol in the organism is either absorbed from animal food or synthesized from metabolic products. After being excreted through bile and the intestinal mucosa, it is reabsorbed, unless it has been transformed into dihydrocholesterol, which is nonabsorbable. Lipoids in vegetable food are nonabsorbable. Under both a mixed and a vegetable dietary regimen the organism excretes cholesterol and dihydrocholesterol into the intestinal tract, cholesterol being reabsorbed to a great extent while dihydrocholesterol is finally excreted in greater quantities. Schönheimer's patient suffered from a lipemia of 2,100 mg. and a hypercholesteremia of 825 mg. per hundred cubic centimeters. Multiple xanthomatous tumors were present in tendons and tendon sheaths, and the scar of an old laparotomy had undergone xanthomatous changes. When the patient was put on a vegetable diet with exclusion of absorb-

able lipoids, the blood cholesterol dropped to 300 mg. per hundred cubic centimeters, but there was no influence on the xanthomatosis. The feces showed a lack of cholesterol and cholesterol derivatives on both a mixed and a vegetarian diet, while dihydrocholesterol could be found up to the unusually high concentration of 10 per cent of the total lipoids in the blood plasma. Schönheimer came to the conclusion that his patient was able to absorb cholesterol from the food, but unable to excrete it. The accumulation of dihydrocholesterol in the blood was an additional proof of deficient excretory function.

Recourse has been had repeatedly to animal experimentation in order to reproduce xanthoma formation by overloading the circulation with lipoids. The basis for this experimental work was furnished by the experience accumulated during the investigation of artificially produced hypertension and atherosclerosis. In the pursuit of those studies it was discovered that herbivorous animals, the rabbit in particular, acquire this condition after feeding on various animal food substances in which cholesterol could be found as the pathogenic agent; feeding with pure cholesterol (Versé) yielded identical results, and hypercholesteremia invariably preceded the hypertension. The anatomic changes found in the hypercholesteremic rabbits were not confined to the arteries, but involved many parenchymatous organs and aggregates of reticulo-endothelial cells, which sometimes assumed the shape of typical foam cells infiltrated with cholesterol esters. The general well-being of the animals was greatly impaired, so that Schönheimer spoke of an "experimental cholesterol disease of the rabbit."

Anitschkow reproduced xanthoma cells in the experiment by creating sterile abscesses in the subcutaneous tissue of hypercholesteremic rabbits. In the granulation tissue limiting these abscesses typical foam cells with doubly refractive lipoids were found.

Weidman was unable to confirm Anitschkow's results. He, furthermore, experimented on hypercholesteremic and on xanthomatous patients by inflicting operative injuries and applying chemical irritation. None of his patients showed xanthomatous scars.

Wustmann injected silicious earth close to the bones of hypercholesteremic rabbits. The granulomas contained cholesterol deposits, but not cells comparable with xanthoma cells.

Hoessli experimented with hypercholesteremic rabbits. The tendo achillis was concussed for eight minutes daily for from four to six weeks. The tendon showed infiltration with cholesterol but no proliferation of foam cells. By no means did the histologic structure resemble the xanthomatous tumors of the tendons of a patient of his who had hypercholesteremia. Lebedew experimented by inserting sterile foreign bodies like cork and sutures saturated with 10 per cent potassium hydroxide into the subcutis of hypercholesteremic rabbits. The first results were negative, but after prolonging the irritation and examining the tissues at a later time, when the inflammation had become more chronic, he could observe typical foam cells containing lipoid droplets. Experiments on normal rabbits were carried out by

making local deposits of cholesterol dissolved in sunflower oil. Here again histologic structures resembling xanthofibromas could be discovered from two and a half to three months after the injection of cholesterol.

Basten used an emulsified gallstone for local deposits in the ears and subcutis of a normal rabbit. He found large pale cells containing cholesterol esters as early as seven days after injection. These cells were derived from connective tissue cells and contained cholesterol ester.

As interesting as these experimental results may be, they are not uniform nor are they obtained under conditions that parallel human disorders sufficiently to make them applicable to the problem of xanthoma. In this connection it might be necessary again to emphasize certain differences in the lipoid metabolism of the rabbit and the human being which have been brought out by the extensive experimental work with cholesterol feeding. Man and omnivorous animals react to an alimentary excess of fat with a transitory and visible lipemia; i. e., the blood plasma becomes milky because of the accumulation of fat droplets. On repetition of the heavy doses of fatty substances the organism gains corrective faculties and soon no visible or concealed lipemia of greater extent occurs. The opposite behavior is observed in herbivorous animals. Here a single fat feeding does not produce lipemia, but a prolonged feeding with fats in combination with cholesterol eventually produces a lipemic condition, which at first can be detected only by chemical determination, but later on is disclosed by a clouding of the blood plasma. Feeding cholesterol alone or feeding neutral fats alone is not conducive to a visible lipemia. But every increase of cholesterol in the blood is associated with an increase of neutral fats regardless of the source of the hypercholesteremia. Likewise, any lipemia caused by pathologic metabolism or by overfeeding with neutral fats is accompanied by a rise of blood cholesterol. These findings point to a complexity of the metabolism of lipoid substances and create considerable doubt as to whether cholesterol has an independent metabolism. They suggest further that lipoids may circulate emulsified in varying degree, sometimes coarse enough to become visible in the blood plasma, sometimes in very fine droplets not interfering with its transparency. These facts have also been exploited for the theory of the etiology of xanthoma.

Experimental work has furthermore been carried out with regard to the histogenesis of foam cells. Biedermann and Höfer studied, in tissue culture, a specimen of bone marrow from a patient with Hand-Christian-Schüller's disease whose blood showed 238 mg. of cholesterol per hundred cubic centimeters. The appearance of the growing cells suggested their origin from the reticulo-endothelium. They developed into typical foam cells. This tissue culture was prepared with the hypercholesteremic serum of the patient. Fibroblasts from chickens grown in

the same medium failed to develop into foam cells. This indicates that the chemical medium is not so important a factor as are the essential metabolic characteristics of the cells themselves.

Summarizing the foregoing histochemical discussion, we may conclude that:

1. Unphysiologic concentrations of cholesterol or cholesterol esters in the blood occurring either primarily or secondarily to other known humoral disorders are sometimes associated (but not necessarily so) with xanthomatous foam cell tumors or granulomas.

2. Xanthomatous tissue changes may occur without increase of cholesterol in the blood.

3. Several attempts have been made by various authors to defend the theory of the etiologic relation between blood cholesterol and xanthoma in spite of the fact that hypercholesteremia is not apparent in a considerable number of typical cases. Other investigators deny such an etiologic relationship.

4. In diabetic xanthomatosis an involution of the xanthomatous lesions can be regularly brought about by antidiabetic treatment that occasions a lowering of the lipocholesteremia. In other forms of xanthomatosis, however, although the accompanying lipocholesteremia may sometimes be favorably influenced by a prolonged dietary regimen, an improvement of the pathologic tissue changes may not necessarily follow.

5. The etiology of various forms or types of xanthomatosis is still to be determined.

BIBLIOGRAPHY

Abrikossoff, A., and Herzenberg, A.: Virchows Arch. f. path. Anat. **274**:146, 1929.

Adair, F. E.; Pack, G. T., and Farrior, J. J.: Am. J. Cancer **16**:1104, 1932.

Addison, T., and Gull, W.: Guy's Hosp. Rep. **7**:265, 1851.

von Albertini, A., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Vienna, Julius Springer, 1929, vol. 9, pt. 1, p. 508.

Anitschkow, N.: Arch. f. Dermat. u. Syph. **120**:627, 1914.

Arndt, H. J.: Verhandl. d. deutsch. path. Gesellsch. **20**:143, 1925.

Arning, E.: Deutsche med. Wchnschr. **36**:1885, 1910.

Arzt, L.: Arch. f. Dermat. u. Syph. **126**:809, 1919.

Aschoff, L.: Beitr. z. path. Anat. u. z. allg. Path. **47**:1, 1910; Ergebn. d. inn. Med. u. Kinderh. **26**:1, 1924.

Baar, H.: Ztschr. f. Kinderh. **38**:682, 1924.

Balzer, F.: Arch. de physiol. norm. et path. **4**:65, 1884.

Basten, G.: Virchows Arch. f. path. Anat. **220**:176, 1915.

Beitzke, H.: Beitr. z. path. Anat. u. z. allg. Path. **69**:400, 1921.

Biedermann, W., and Höfer, K.: Arch. f. exper. Zellforsch. **10**:93, 1930.

Bross, K.: Virchows Arch. f. path. Anat., supp., vol. 227, 1920.

Burger, M., and Reinhart, A.: Ztschr. f. exper. Med. **7**:119, 1918.

Carry: Lyon méd. **32**:225, 1879.

Chalatow, S. S.: Die anisotrope Verfettung im Lichte der Pathologie des Stoffwechsels, Jena, Gustav Fischer, 1922; cited by von Albertini.
Chambard, E.: Arch. de physiol. **6**:691, 1879.
Chauffard, A., and Laroche, G.: Semaine méd. **30**:241, 1910.
——Laroche, G., and Grigaud, A.: Soc. de biol. **70**:855, 1911.
Cheatle, G. L., and Cutler, M.: Tumors of the Breast, Philadelphia, J. P. Lippincott Company, 1932, p. 307.
Chester, W.: Virchows Arch. f. anat. Path. **279**:561, 1931.
Chiari, H.: Ergebn. d. allg. Path. u. path. Anat. **24**:396, 1931; Virchows Arch. f. path. Anat. **288**:527, 1933.
Chvostek: Ztschr. f. klin. Med. **73**:479, 1911.
Coenen, H.: Arch. f. klin. Chir. **78**:711, 1906.
Corten, M. H.: Frankfurt. Ztschr. f. Path. **23**:389, 1920.
Davison, C.: Arch. Neurol. & Psychiat. **30**:75, 1933.
Dietrich, A.: Virchows Arch. f. path. Anat. **212**:119, 1913.
——and Kleeberg, J.: Ergebn. d. allg. Path. u. path. Anat. **11**:977, 1924.
Dor, L.: Rev. de chir. **18**:1089, 1898.
Dubs, I.: Centralbl. f. allg. Path. u. path. Anat. **34**:145, 1923.
Engman, M. F., and Weiss, R. S.: Arch. Dermat. & Syph. **8**:625, 1923.
Epstein, E.: Klin. Wchnschr. **10**:1601, 1931.
Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1928, pp. 192 and 801.
Fagge, C. H.: Tr. Path. Soc., London **24**:242, 1872-1873.
Fahr, T.: Centralbl. f. allg. Path. u. path. Anat. **30**:609, 1920.
Finney, W. P.; Montgomery, H., and New, G. B.: J. A. M. A. **99**:1071, 1932.
Fleissig, J.: Deutsche Ztschr. f. Chir. **122**:239, 1913.
Gaal, A. M.: Ztschr. f. klin. Med. **113**:349, 1930.
Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, vol. 1. p. 136.
Geber, E., and Simon, O.: Arch. f. Dermat. u. Syph. **4**:305, 1872.
Geyer: Arch. f. Dermat. u. Syph. **40**:37, 1897.
Greenbaum: Arch. Dermat. & Syph. **13**:291, 1926.
Hagensen, C. D.: Am. J. Cancer **16**:1076, 1932.
Hallopeau, H.: Ann. de dermat. et syph. **4**:935, 1893.
Harbitz, F.: Arch. Path. **4**:507, 1927.
Hardaway, W. A.: St. Louis Cour. Med. **12**:289, 1884.
Hebra, F., and Kaposi, M.: Lehrbuch der Hautkrankheiten, Stuttgart, Ferdinand Enke, 1874, vol. 2, p. 258.
Hedinger: Schweiz. med. Wchnschr. **4**:828, 1923.
Henschen, Folke: Acta paediat. (supp. 6) **12**:1, 1931.
Herrmann, F., and Nathan, E.: Arch. f. Dermat. u. Syph. **152**:575, 1926.
Herzenberg, H.: Virchows Arch. f. path. Anat. **269**:614, 1928.
Heuer, in Lewis, Dean: Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1930, vol. 5, chap. 5.
Heurteaux, M. A.: Arch. gén. de méd. **167**:40 and 160, 1891.
Hirsch, A.: Frankfurt. Ztschr. f. Path. **10**:408, 1912.
Hoessli, H.: Beitr. z. klin. Chir. **95**:198, 1914.
Janik, A.: Ann. Surg. **85**:897, 1927.
Joel, E.: Klin. Wchnschr. **3**:1965, 1924.
Kammer: Ein Fall von Riesenzellen-Xanthosarkoma, Inaug. Dissert., Freiburg, 1909.

Kaposi, M.: Wien. med. Wchnschr. **22**:169 and 192, 1872.
Karoliny, L.: Virchows Arch. f. path. Anat. **264**:305, 1927.
Katsurashima, T.: Mitt. u. allg. Path. **7**:241, 1932.
Kinoshita, M.: Ztschr. f. Urol. **14**:192, 1920.
Kirch, E.: Beitr. z. path. Anat. u. z. allg. Path. **70**:75, 1922; Klin. Wchnschr. **3**: 1425, 1924.
Kneringer, E., and Priesel, A.: Virchows Arch. f. path. Anat. **241**:475, 1923.
Knowles, F. C., and Fischer, H. N.: J. A. M. A. **75**:1557, 1921.
Kolodny, A.: Surg., Gynec. & Obst. **44**:1, 1927.
Krecke: Zentralbl. f. Chir. **54**:2030, 1927.
Krogius, A.: Acta chir. Scandinav. **55**:363, 1923.
Krzysztalowicz, F.: Monatsh. f. prakt. Dermat. **29**:201, 1899.
Kusnetzowsky, N. J.: Arch. f. klin. Chir. **124**:13, 1923.
Landois, F., and Reid, M.: Beitr. z. klin. Chir. **95**:56, 1914.
Lazarewa, A.: Fortschr. a. d. Geb. d. Röntgenstrahlen **45**:692, 1932.
Lebedew, A. J.: Dermat. Wchnschr. **59**:1343 and 1372, 1914.
Lehzen, G., and Knauss, K.: Virchows Arch. f. path. Anat. **116**:85, 1889.
Leupold, E.: Der Cholesterinstoffwechsel, in Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1928, vol. 5, p. 1095.
Lobeck, E.: Arch. f. klin. Chir. **141**:540, 1926.
Low, R. C.: Brit. J. Dermat. **22**:109, 1911.
Lubarsch, O.: Deutsche med. Wchnschr. **44**:484, 1918; Virchows Arch. f. path. Anat. **269**:823, 1928.
McGraw, A. B.: Am. J. Cancer **18**:345, 1933.
McWorther, J. E., and Weeks, C.: Surg., Gynec. & Obst. **40**:199, 1925.
Major, R. H.: Bull. Johns Hopkins Hosp. **35**:27, 1924.
Mandl, F.: Zentralbl. f. Chir. **53**:260, 1926.
Miller, E. M.: Ann. Surg. **80**:256, 1924.
Mook, W. H., and Weiss, R. S.: Arch. Dermat. & Syph. **8**:19, 1923.
Morris, Crocker, Sangster and Hutchinson: Tr. Path. Soc., London **34**:278, 1883.
Murchison: Tr. Path. Soc., London **20**:187, 1869.
Nöthen: Frankfurt. Ztschr. f. Path. **23**:471, 1920.
von Noorden, K.: Die Zuckerkrankheit und ihrer Behandlung, ed. 6, Berlin, A. Hirschwald, 1912, p. 181.
Ollerenshaw, R.: Brit. J. Surg. **10**:466, 1923.
Pavy, F. W.: Guy's Hosp. Rep. **12**:276, 1866.
Petri, E.: Frankfurt. Ztschr. f. Path. **27**:507, 1922; Centralbl. f. allg. Path. u. path. Anat. **54**:113, 1932.
Pick, L.: Monatsh. f. prakt. Dermat. **46**:545, 1908; Berl. klin. Wchnschr. **37**: 1679, 1908; Ergebn. d. inn. Med. u. Kinderh. **29**:317, 1925; Virchows Arch. f. path. Anat. **274**:152, 1929; Am. J. M. Sc. **185**:453 and 601, 1933.
Pinkus, F., and Pick, L.: Deutsche med. Wchnschr. **34**:1426, 1903.
Poensgen, A.: Virchows Arch. f. path. Anat. **91**:350, 1883.
Pollitzer, S., and Wilde, U. J.: J. Cutan. Dis. **30**:225, 1912.
Proescher, F., and Meredith, E. W.: Surg., Gynec. & Obst. **9**:578, 1909.
Pye-Smith, P. H.: Tr. Path. Soc., London **24**:250, 1873.
Quinquaud, C. E.: Bull. Soc. clin. de Paris, 1878.
Rayer, P.: Traité des maladies de la peau, ed. 2, Paris, 1836.
Reverdin, J.: Rev. méd. de la Suisse Rom. **5**:671, 1885.
Robertson, S. H., and Warren, S.: Arch. Path. **15**:193, 1933.
Rosenbloom, J.: Arch. Int. Med. **12**:395, 1913.

Rosenthal, F., and Braunisch, R.: Ztschr. f. klin. Med. **92**:429, 1921.
Rowland, R. S.: Anomalies of Lipid Metabolism, Oxford Medicine, New York, Oxford University Press, 1921, vol. 4.
Saralegui, A. F., and Lascano Gonzales, J. C.: Bol. y trab. de la Soc. de cir. de Buenos Aires **15**:888, 1931.
Schaaf, F., and Werner, A. J.: Arch. f. Dermat. & Syph. **162**:217, 1930.
Schlagenhaufer, F.: Centralbl. f. allg. Path. u. path. Anat. **18**:897, 1907.
Schmidt, E.: Dermat. Ztschr. **21**:137, 1914.
Schönheimer, R.: Virchows Arch. f. path. Anat. **249**:1, 1924; Ztschr. f. klin. Med. **123**:749, 1933.
Schröder, F.: Arch. f. klin. Chir. **168**:118, 1931.
Schulte, E.: Beitr. z. path. Anat. u. z. allg. Path. **61**:570, 1916.
Seyler: Virchows Arch. f. path. Anat. **239**:20, 1922.
Sickemeier, E.: Frankfurt. Ztschr. f. Path. **14**:428, 1914.
Siemens, W. H.: Arch. f. Dermat. u. Syph. **136**:159, 1921.
Smith, C. H.: Surg., Gynec. & Obst. **14**:550, 1912.
Smith, W. F.: J. Cutan. Med. **3**:241, 1869-1870.
Sosman, M. C.: Am. J. Roentgenol. **23**:581, 1930.
Spiess, P.: Frankfurt. Ztschr. f. Path. **13**:1, 1913.
Sprenger, W.: Arch. f. klin. Chir. **169**:683, 1932.
Toepfer, G.: Arch. f. Dermat. u. Syph. **40**:3, 1897.
Török, L.: Ann. de dermat. et syph. **4**:1109, 1893.
Touton: Vrtljschr. f. Dermat. u. Syph. **17**:3, 1885.
Tramonto, V., and Fittipaldi, C.: Tumori **4**:469, 1930.
Umber: Berl. klin. Wchnschr. **53**:829, 1916.
Unna, P. G.: Die Histopathologie der Hautkrankheiten, in Lehrbuch der pathologischen Anatomie, Berlin, A. Hirschwald, 1894, p. 953.
Versé, M.: Beitr. z. path. Anat. u. z. allg. Path. **52**:1, 1912; Verhandl. d. deutsch. path. Gesellsch. **20**:67, 1925.
de Vincentiis, C.: Riv. clin. di Bologna **3**:481, 1883.
Virchow, R.: Virchows Arch. f. path. Anat. **52**:504, 1871.
Waldeyer: Virchows Arch. f. path. Anat. **52**:318, 1871.
Weidman, F. D.: Arch. Dermat. & Syph. **15**:659, 1927.
——and Freeman, W.: Arch. Dermat. & Syph. **9**:149, 1924.
Weil, S.: Beitr. z. klin. Chir. **93**:617, 1914; Berl. klin. Wchnschr. **52**:129, 1915.
Wells, H. G.: Chemical Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1920, p. 467.
Wessen, N.: Acta chir. Scandinav. **53**:621, 1921.
Westphal, K.: Ztschr. f. klin. Med. **113**:323, 1930.
Wile, U. J.; Eckstein, H. C., and Curtis, A. C.: Arch. Dermat. & Syph. **19**:35, 1929; **20**:489, 1929.
Wilson, W. J. E.: A Practical and Theoretical Treatise on the Diagnosis, Pathology and Treatment of Diseases of the Skin, ed. 5, Philadelphia, Blanchard & Lea, 1863, p. 618.
Wolodin, A. N., cited by von Albertini.
Wustmann, O.: Ztschr. f. d. ges. exper. Med. **46**:731, 1925.
Zeyland, J., and Dega, W.: Arch. f. klin. Chir. **150**:310, 1920.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

INACTIVATION OF INSULIN BY NORMAL AND DIABETIC BLOOD. PETER T. BLACK, Brit. J. Exper. Path. **14**:318, 1933.

Insulin incubated with serum or with laked cells or with cytolysed leukocytes loses some part of its power to lower the blood sugar and produces convulsions in fasting rabbits when the mixture is injected subcutaneously. Insulin incubated with laked cells loses some part of its power to lower the blood sugar when injected intravenously into rabbits. This is probably due to destruction of the insulin by an enzyme other than trypsin. The inactivating substance does not readily pass from the cells to the plasma. Insulin incubated with heparinized whole blood retains its power to lower the blood sugar when injected intravenously into rabbits. This is also true of insulin incubated with intact red cells or leukocytes. Blood from diabetic patients, even from those displaying resistance to insulin, had no more than normal power to destroy insulin in any of these experiments. This investigation, therefore, does not support the view that the symptoms of diabetes are due to destruction of insulin in the circulation.

AUTHOR'S SUMMARY.

BIOLOGIC TEST FOR HODGKIN'S DISEASE. C. E. VAN ROOYEN, Brit. M. J. **1**:644, 1933.

Gordon found that the intracerebral inoculation of rabbits and guinea-pigs with suspensions of lymph glands from persons with Hodgkin's disease was followed in a few days by spastic paralysis of the hindlimbs, rigidity, ataxia and muscular weakness. Of five cases of Hodgkin's disease in which this test was made, there were three in which a positive reaction was observed; the reaction in one was doubtful and in one, negative. The reaction cannot be elicited by the use of normal, lymphosarcomatous, leukemic or tuberculous lymphatic tissue. Neither can it be brought about by the intracerebral inoculation of dead bacteria, streptococcus toxin, sterile milk, peptone water, sodium nucleate or finely powdered glass.

JACOB KLEIN.

SOME EFFECTS OF ARTIFICIAL PNEUMOTHORAX ON THE CIRCULATION. R. HILTON, J. Path. & Bact. **37**:1, 1933.

It is suggested that the cause of the first increase in minute volume observed after the induction of pneumothorax is due to the increased inspiratory efforts and probably to anoxemia. The subsequent fall in minute volume may be explained by a diminished mechanical efficiency of the breathing when the pleural cavity is full of air, with a consequent interference with the return of venous blood to the heart.

AUTHOR'S SUMMARY.

EFFECT OF EXPERIMENTAL PORTAL CONGESTION ON THE ABSORPTION AND EXCRETION OF WATER. J. MCMICHAEL and F. H. SMIRK, J. Path. & Bact. **37**:81, 1933.

Rats in which the portal vein has been obstructed show, on the day after operation, a diminished rate of absorption of water from the alimentary tract and a delayed diuresis. Venous anastomoses open up in the course of the week following operation, and the delayed absorption rate improves but does not return to normal. The diuresis curve may at this time have returned to normal despite the moderate delay in the absorption of water

AUTHORS' SUMMARY.

THE FUNCTIONS OF BRUNNER'S GLANDS AND THE PYLORIC END OF THE STOMACH. H. W. FLOREY and H. E. HARDING, J. Path. & Bact. **37**:431, 1933.

A description is given of a method of collecting a considerable amount of the secretion of Brunner's glands in the rabbit. This secretion is very alkaline—p_H 8, rapidly rising to p_H 9 on exposure to air—and is at least equivalent to tenth-normal sodium bicarbonate, and in most cases more. The alkalinity is due to its content of bicarbonates. The fluid is of the consistency of the white of egg and clear or slightly opalescent. Brunner's glands of the rabbit, cat, guinea-pig and rat are activated by passing hydrochloric acid over them. Those of the rabbit respond to stimulation with oil of mustard. The relationship of this activity to the extrinsic innervation is discussed. The significance of this alkaline secretion for the protection of the gastric and duodenal mucosae is indicated, and a possible relationship between a failure of secretion and the production of peptic ulcer is suggested.

AUTHORS' SUMMARY.

INFLUENCE OF COLLOIDAL IRON AND ALTITUDE ON EXPERIMENTAL ANEMIA. WALTER HEIMANN, Beitr. z. Klin. d. Tuberk. **82**:418, 1933.

Anemia was induced in rabbits by the injection of acetylphenylhydrazine. The rate of spontaneous recovery was then compared with that following intravenous administration of active colloidal iron oxide. No significant acceleration of regeneration was observed. The experiment was repeated at an altitude of 3,000 meters and also in a low pressure chamber. In both, spontaneous recovery occurred at twice the rate of that in the lowlands. Again, colloidal iron oxide administered intravenously did not accelerate the process. In fact, in large doses it definitely hindered regeneration.

AARON EDWIN MARGULIS.

TISSUE CULTURE STUDIES ON BLOOD VESSELS AND SEROUS MEMBRANES. WERNER SCHOPPER, Beitr. z. path. Anat. u. z. allg. Path. **88**:451, 1932.

Tissue was obtained from guinea-pigs, and the cover glass method of Maximow was followed. As a medium, plasma of guinea-pigs with heparin and embryonal extract was used. Normal omentum, omentum after the injection of infusorial earth, vena cava and aorta were studied. Small blood vessels were obtained from the leptomeninges. The tissue cultures were observed during from ten to twelve subcultures.

The growth of the serous cells lining the surface of the omentum in the early cultures is epithelial-like. They form membranes consisting of large, flat, surface cells. In later stages, they more and more resemble fibroblasts. In tissue defects, the serous cells do not regenerate from the fibroblasts of the omentum. The undifferentiated mesenchymal cells which are distributed diffusely in the omentum and the adventitial cells surrounding capillaries form macrophages which are able to engulf neutral red. Under certain conditions, the macrophages may develop into fibroblasts.

Small lymphocytes emigrating from the sheaths of the blood vessels degenerate after a few days. Buds of endothelial cells grow out of capillaries into the tissue and into the surrounding culture medium. These buds are mostly solid and consist of slender endothelial cells. In later cultures single endothelial cells are found, resembling fibroblasts. The muscle tissue of the larger blood vessels in the omentum does not proliferate, but may be seen well preserved for thirty-five days.

If infusorial earth is added to the tissue culture in too large amounts, cell proliferation will be stopped. Also, small doses will lessen the epithelial-like growth of the serous cells. The emigration of macrophages is, however, increased. Foreign body giant cells form by fusion of macrophages. Typical foreign body tubercles surround deposits of infusorial earth. The omentum obtained from animals after intraperitoneal injection of infusorial earth shows a much more active

cell proliferation than in normal tissue. There are many foreign body giant cells, wandering cells, lymphocytes and serous cells present. The serous cells grow either as an epithelial-like membrane or as fibroblasts.

In cultures of aorta and vena cava, the adventitial cells grow first in a circular arrangement; later they grow into the medium like typical fibroblasts and develop fine fibrils. The latter originate only from cells. The endothelial cells grow into the lumen and may cause obliteration of the lumen by producing fibrils.

The cerebral arteries were dissected carefully from the surrounding tissue prior to culture. The endothelial cells are very active, producing solid and tubular buds which may form a network. Small artificial defects in the wall of the vessel are filled out by proliferating endothelial cells. If a blood vessel is cut in two, the stumps will unite, if these are lying close together. If the stumps are far apart, union is made impossible because adventitial cells will grow into the defect before endothelial cells show proliferation.

C. ALEXANDER HELLWIG.

THE PROBLEM OF JAUNDICE CAUSED BY TOLYLENEDIAMINE. H. H. GREENE and W. SCHAAL, Beitr. z. path. Anat. u. z. allg. Path. **89**:61, 1932.

In dogs, injection of tolylenediamine caused hemolysis and also degeneration of the intrahepatic bile ducts. The degree of hemolysis is less after removal of the spleen. The jaundice occurring after the injection of tolylenediamine apparently has three explanations: 1. It may be due to the degeneration of the epithelial cells of the intrahepatic bile ducts. The bile excreted by the liver cells thus passes into the hepatic lymph spaces and from there directly or by way of the thoracic duct into the blood stream. 2. Hemolysis may play a causative rôle in the jaundice, as evidenced by the marked swelling of the Kupffer cells and their phagocytosis of the débris of erythrocytes. 3. The formation of bile thrombi in the bile capillaries of the liver may cause true obstructive jaundice.

C. ALEXANDER HELLWIG.

INFLUENCE OF SALT SOLUTIONS ON THE RENAL TISSUE. H. NIEWIESCH, Beitr. z. path. Anat. u. z. allg. Path. **89**:76, 1932.

Different salt solutions, in various concentrations, were injected into the left renal artery of rabbits and the histologic changes in the left kidney were compared with the normal structure of the other kidney. Calcium chloride, sodium chloride and sodium phosphate (monobasic) produced coagulation necrosis of the epithelial lining of the convoluted tubules. By using higher concentrations of these substances, degeneration of the straight tubules was noticed, whereas the glomeruli were most resistant. A marked leukocytic infiltration was observed in the interstitial tissue surrounding the degenerated tubules. These inflammatory changes are, in the opinion of the author, directly due to irritation by the chemical substances and precede the necrosis of the tubules.

C. ALEXANDER HELLWIG.

EXPERIMENTAL STREPTOCOCCIC ARTHRITIS IN RABBITS. G. WEHRSIG and A. J. WEIL, Beitr. z. path. Anat. u. z. allg. Path. **89**:311, 1932.

Rabbits were given intravenous or intraperitoneal injections of various strains of streptococci. Single and repeated injections, with and without previous sensitization by vaccine, were made, and the resulting lesions in the joints were studied microscopically. The arthritis produced in rabbits by the injection of streptococci did not show the microscopic picture of infectious rheumatism, but resembled septic arthritis as found in man after general infection with pyogenic organisms. The lesions of the joints originated either from the capsule or from the bone marrow beneath the cartilaginous surface of the joint.

C. ALEXANDER HELLWIG.

GLYCOGENOSIS. P. KIMMELSTIEL, Beitr. z. path. Anat. u. z. allg. Path. **91**:1, 1933.

The condition which the author portrays was first described under the name glycogenic hepatonephromegaly by von Gierke in 1929 (*Beitr. z. path. Anat. u. z. allg. Path.* **82**:497, 1929; abstr., ARCH. PATH. **10**:125, 1930); two additional cases were reported by Putschar (*Beitr. z. path. Anat. u. z. allg. Path.* **90**:222, 1932; abstr., ARCH. PATH. **17**:4, 1934). The author's case is the fourth recorded example of this condition, for which he prefers the name "glycogenosis." A child died of acute pharyngitis and bronchopneumonia; the age at death is not stated in the brief clinical summary. Enlargement of the abdomen was noticed by the mother when the child was between 3 and 4 weeks old. At necropsy, the liver extended below the level of the umbilicus and weighed 1,600 Gm. Each kidney weighed 45 Gm., and, as was true in Putschar's cases, was much less enlarged than in von Gierke's case. The liver, cardiac muscle, voluntary muscle and brain contained large quantities of glycogen; the kidneys contained a smaller amount, situated chiefly in the epithelium of the straight tubules. The glycogen did not disappear as rapidly from the liver after death as is usually the case. Although the glycogen of the liver yielded as large a proportion of dextrose on acid hydrolysis as did pure glycogen or the glycogen of normal dog's liver, it yielded a definitely smaller proportion when subjected to diastatic fermentation. The pancreatic islets were histologically normal with the exception of a few that were somewhat enlarged. The two previous observers sought the explanation of the condition in decreased glycogenolytic activity of the liver. In view of the unequal distribution of the glycogen, especially in a single organ like the brain, Kimmelstiel does not accept this suggestion. He postulates a disturbance of carbohydrate metabolism that leads to the formation of a heterotypical form of dextrose, which is polymerized into a form of glycogen that is not readily split by the normal diastatic enzyme.

O. T. SCHULTZ.

Pathologic Anatomy

SPLENOMEGALY AND SPLANCHNOMEGALY. M. MÜHLMANN, Beitr. z. path. Anat. u. z. allg. Path. **90**:180, 1932.

The author reports a case in which marked enlargement of the spleen was associated with increase in the size of the liver, kidneys, testes and lungs, without evidences of acromegaly. The enlargement of the organs was due to hypertrophy of the parenchymatous elements, to an increase in the amount of collagenous, elastic and reticular fibrillated tissues and to an increase in the size of the cells of the reticulo-endothelial system. The lymphatic elements were atrophic. The globus pallidus of the left lenticulate nucleus was about one-third larger than that of the right. Microscopically, it revealed an increased number of glia cells, as compared with the right globus, and a paucity of ganglion cells, which were numerous and large on the right side. Mühlmann then presents epitomes of four additional cases of what he holds to be the same condition, although insufficient attention was paid to the brain. Finally, he gives brief summaries of sixteen cases collected during his earlier work in Baku, which cases he had at that time looked on as Banti's disease. Splanchnomegaly, of which splenomegaly is only a part, is a constitutional systemic disease in which the hypertrophy of the organ is due to abnormal functioning of the central vegetative nervous system. This conception is supported by Mühlmann's previously propounded theory that the hyperplasia of tumor formation is the result of the activity of the central vegetative nervous system, for which theory, it may be parenthetically remarked, there does not seem to be any strong basis of support.

O. T. SCHULTZ.

CONGENITAL GLYCOGENIC HYPERTROPHY OF THE HEART. W. PUTSCHAR, Beitr. z. path. Anat. u. z. allg. Path. **90**:222, 1932.

A child died at the age of 4 months of bilateral bronchopneumonia. At the age of 12 days, generalized edema was noted, but no abnormality of the heart was detected. At 13 weeks of age, it was noted that the liver was enlarged, and on

admission to the hospital marked enlargement of the heart was detected. At necropsy, the heart was found greatly enlarged, weighing 110 Gm. The wall of the left ventricle varied from 7 to 21 mm. in thickness, that of the right ventricle from 6 to 12 mm. The liver was moderately enlarged and weighed 240 Gm. Each kidney weighed 25 Gm. The increase in the size of the heart was due to marked infiltration of the muscle fibers by glycogen. The liver cells and the epithelium of the convoluted tubules of the kidney were vacuolated by glycogen. The case is held to belong to a group of which von Gierke described two examples in 1929 as congenital glycogenic hepatonephromegaly. Von Gierke considered the condition one of abnormal glycogen metabolism, which he likened to the diseases characterized by lipoid infiltration, namely, Gaucher's disease, Niemann-Pick's disease and Hand's (Schüller-Christian's) disease. In Putschar's report there is no note of histologic examination of the pancreas. In a brief note he mentions the case of a 3 year old child in whom abnormal carbohydrate metabolism was detected during life by chemical studies. Biopsy revealed that the enlargement of the liver detected clinically was due to glycogen infiltration.

O. T. SCHULTZ.

OSSIFICATION OF THE SACRAL INTERVERTEBRAL DISKS. A. S. JACOBSON and H. DRIVER, Beitr. z. path. Anat. u. z. allg. Path. **90**:233, 1932.

The work here reported comes from Schmorl's institute, where the vertebral column is removed and subjected to study as a routine procedure. It is based on the study of 258 sacrums of persons of the second to ninth decades, inclusive. The anatomists cited state that ossification of the sacral intervertebral disks begins during the eighteenth year of life and usually leads to bony union of the vertebral bodies by the twenty-fifth year. The authors found that ossification was already evident during the second decade of life, but that even so late as the ninth decade the process was not complete. Ossification became progressively more marked in a caudal direction. Complete ossification of the first, second and third disks was noted in no instance during the second decade and occurred in 10, 46 and 53 per cent, respectively, in the ninth decade. Only the three upper disks are included in the tabulations, because the fourth and fifth sacral vertebrae were not removed in every case. Partial and complete ossification of the first, second and third disks was observed in 4, 15 and 25 per cent, respectively, during the second decade, in 65, 89 and 100 per cent during the eighth decade and in 75, 100 and 100 per cent during the ninth decade. Ossification is due not to the ingrowth of blood vessels into the disks, but to the invasion of the disks by the marrow of the vertebral bodies. The disk is then transformed partly or completely into spongy bone. The process is looked on as phylogenetic.

O. T. SCHULTZ.

THE NEUROMUSCULAR APPARATUS OF THE APPENDIX IN CHRONIC APPENDICITIS. L. SCHACK, Beitr. z. path. Anat. u. z. allg. Path. **90**:392, 1932.

Schack's description of changes in the neuromuscular apparatus of the appendix is preceded by a description of this apparatus in the normal organ. The technical methods of Masson were used, and this author's conception of the normal neuromuscular apparatus is confirmed. The apparatus consists of four parts: the external and internal muscular coats with the plexus of Auerbach; the musculonervous complex of the submucosa, which includes Meissner's plexus; the muscularis mucosae, which has its own nerve plexus, and the mucosa with the periglandular plexus of Masson. Seventy-six of 150 chronic appendixes taken at random revealed changes in the neuromuscular apparatus similar to those described by Masson in what the latter considered a characteristic type of appendical involvement which he termed neurogenous appendicitis. The changes noted were hypertrophy or localized hyperplasia of the neuromuscular apparatus. Such changes were always associated with other changes that were the result of previous active inflammation. Schack therefore contends that Masson's neurogenous appendicitis is not a specific type of involvement, but is a result of inflammation.

Hypertrophy of the neuromuscular apparatus is a work hypertrophy, brought about by increased resistance to movement of lymph and secretion resulting from structural alterations caused by inflammation. The localized hyperplasias are minute neuromas that are the result of the inflammatory stimulus. They correspond to the small neuromas frequently seen in the chronically inflamed submucosa of the gallbladder and stomach. Schack detected axis-cylinders in such neuromas and observed degenerative changes of the neurofibrils at the center of the neuromas. There was nothing characteristic in the clinical symptomatology that might be correlated with the changes in the neuromuscular apparatus.

O. T. SCHULTZ.

THE CHROMAFFIN CELLS OF THE APPENDIX. L. SCHACK, Beitr. z. path. Anat. u. z. allg. Path. **90**:441, 1932.

In a profusely illustrated article, Schack discusses the embryogenesis, the emigration, the topography, the morphology, the relationship to muscular and nerve tissues, the quantitative distribution in various types of appendicitis, the special pathologic process and the oncology of the chromaffin cells of the appendix. In the fetal appendix the cells are seen first in the epithelium of the crypts and are of epithelial origin. They emigrate early into the neuro-epithelial syncytium, the presence of which was first described by Masson and is confirmed by Schack, at the bottom of the crypts. From here the cells wander more deeply into the mucosa, retaining a relationship to the neuromuscular apparatus. In the normal appendix they occur in small numbers in the muscularis mucosae, and a few are seen in the submucosa. Single cells have the morphology of ganglion or glia cells. They are impregnated by silver and stained by chrome salts and by acid fuchsin. The cells belong to a group that includes the chromaffin cells of the suprarenal medulla and the melanophores of the skin. The chromaffin cells of the appendix are believed to have an endocrine function which acts on that portion of the neuromuscular apparatus not concerned in the emptying of the appendix. The neurotropic action of the cells manifests itself in growth of neurofibrils. The cells are increased in number in the pathologic appendix, but only when the changes are such as to warrant the conclusion that the appendix has been previously inflamed. These changes include the neuromuscular hypertrophy to which Schack has called attention in a preceding article (*Beitr. z. path. Anat. u. z. allg. Path.* **90**:392, 1932). In the localized neuromuscular hyperplasia of the obliterated appendix, the chromaffin cells are increased in number in the neuromatous areas. In a carcinoid of the appendix, which is considered a tumor-like maldevelopment comparable to nevus of the skin, the neurotropic action of the chromaffin cells was evident by their growth in and along Auerbach's plexus and by increased neurofibril formation in the plexus.

O. T. SCHULTZ.

RELATIVE FREQUENCY OF CALCIFICATION OF THE MITRAL RING. G. MARTENS, Beitr. z. path. Anat. u. z. allg. Path. **90**:497, 1932.

The relative frequency of deposition of calcium in the mitral ring was studied in 1,000 hearts, equally distributed between the two sexes. Calcification was detected in 87 (8.7 per cent) of the hearts. It occurred three times as frequently in women as in men, and was noted at an earlier age in women, 54 years for women as compared with 59 years for men. The condition reached its highest frequency in the age period of from 71 to 74 years. Calcification of the mitral ring was associated with hyperostosis of the frontal bone and calcification of the intervertebral disks. The three processes are looked on as regressive changes, which are probably the result of alterations in calcium metabolism that occur with advancing years.

O. T. SCHULTZ.

THROMBOSIS OF THE HEPATIC VEIN. L. BERK, Beitr. z. path. Anat. u. z. allg. Path. **90**:509, 1932.

The two cases briefly reported, both in women aged 41, were identical clinically and pathologically. In each there were ascites, edema of the lower extremities and a visible collateral venous circulation of the abdomen. At necropsy, there was found organizing mural thrombosis of a portion of the inferior cava 2 cm. long at the region of the mouth of the hepatic vein. The cava was occluded by fresh thrombus, which in one case extended into the iliac and femoral veins. The hepatic vein in each instance was occluded by fresh thrombus. The portal vein was not thrombosed. Syphilis was excluded in each case. These cases differ from the primary endophlebitic thrombosis of the hepatic vein described by Chiari, in that the thrombosis of the hepatic vein was secondary to an older, localized thrombotic process in the cava. As the cause of the latter process, mild trauma is postulated, such as might arise from attacks of coughing.

O. T. SCHULTZ.

EARLY CHANGES AND EVIDENCES OF LATE RESORPTION IN THE LESIONS OF GOUT. G. POMMER, Beitr. z. path. Anat. u. z. allg. Path. **90**:513, 1933.

Each of the first eight paragraphs, which together make up two of the seven pages of Pommer's article, consists of but a single sentence, a fact that should make for easy reading were it not for the further facts that each of these paragraphic sentences consists of from twenty-five to sixty-seven words and that each sentence contains from three to seven compound German words of from fifteen to twenty-five letters each. So much for statistics, which drove the abstractor to a rereading of "Sartor Resartus" and to renewed acquaintance with Herr Teufelsdroeck. Pommer describes the early reactions and some late resorptive changes of the gouty lesion, which he believes did not receive adequate description in his "Gelenkgichtuntersuchungenmonographie." In the early lesions it is necessary to distinguish between those that arise between the fiber bundles of the tendons and those that arise within the bundles. The interfascicular deposition of urates leads to a productive inflammatory reaction about the deposit. In the intrafascicular deposition of urates, such inflammatory reaction is absent until the lesion reaches such a size that it encroaches on the interfascicular tissue. In older lesions that have undergone partial fibrosis or calcification, or even ossification, two forms of resorption are evident. Lacunar resorption, associated with the formation of foreign body giant cells, occurs at the surface of the deposit. In other instances, the mass becomes hollowed out or canalized by central resorption.

O. T. SCHULTZ.

COMPRESSION OF THE CORD BY A VERTEBRAL HEMANGIOMA. E. SCHERER, Beitr. z. path. Anat. u. z. allg. Path. **90**:521, 1933.

Small, sometimes multiple, hemangiomas of the vertebral bodies were noted in 409 (10.7 per cent) of 3,829 vertebral columns examined in the Schmorl institute. These lesions produce no clinical effects. More widespread hemangiomatous involvement of a vertebral body leading to compression of the cord is relatively rare. The author summarizes twelve such cases from the literature and adds one of his own. The patient was a woman, aged 59, who began to be troubled with pain and weakness of the lower extremities two months before hospitalization for operation. On admission, there was complete sensory and motor paralysis below the tenth dorsal segment. The roentgenographic diagnosis was hemangioma of the seventh thoracic vertebra. Resection of the laminae and spinous processes of the sixth, seventh and eighth vertebrae, which had been preceded on the previous day by heat coagulation, resulted in slight improvement, but within eight weeks paralysis was again as complete as before the operation. Death occurred four months after operation. The portions of the seventh vertebra removed at operation and the rest of the vertebra removed at necropsy were the seat of a cavernous hemangioma that had led to atrophy of some of the spongy osseous trabeculae and

to the formation of osteoid tissue. The spinal canal was greatly narrowed. The dura was not involved. Transformation of capillaries into cavernous spaces was evident in the peripheral portions of the hemangioma. Formation of vessels by endothelial budding and transformation of the mesenchyme of the marrow into vessels were not seen.

O. T. SCHULTZ.

FIBROUS INDURATION OF THE HILAR LYMPH NODES OF THE LUNG. W. GIESE, Beitr. z. path. Anat. u. z. allg. Path. **90**:555, 1933.

A review of the literature relating to silicosis and indurative tuberculosis of the lung precedes the detailed description and discussion of Giese's study of induration of the bronchial lymph nodes. The findings that he reports are based in the main on the histologic study of human nodes and lungs, but in part also on experimentation on animals. Fibrous induration of the bronchial nodes may be due either to silicosis or to tuberculosis, the two processes being readily distinguished microscopically. The two processes may be combined. Inoculation into animals revealed that in every instance in which tuberculosis developed in the animal the tuberculous character of the process in the human nodes could be detected histologically. Silicosis may lead to nodular or diffuse induration of the nodes, the former being the result of the transport to the nodes of larger amounts of stone dust. The process begins as reticulo-endothelial hyperplasia in the subcapsular follicles, which are transformed into hyaline, densely fibrous nodules. Diffuse induration, which is due to fibrosis of the reticulum, may be associated with the nodular form or may occur alone; the latter results from small quantities of stone dust. The inorganic ash of incinerated nodes was from five to ten times greater in silicotic and tuberculous indurated nodes than in normal nodes of the same age period. The high ash content of tuberculous indurated nodes is due to the chronicity of the process and to increased phagocytosis of dust by the tuberculous granulation tissue. In both silicotic and tuberculous nodes, the dense fibrous tissue may undergo degeneration, softening and organization or calcification. The pleural lymph nodes undergo the same changes as the hilar nodes; in both, silicotic induration can be differentiated histologically from that due to tuberculosis. Perforation of an indurated node into a bronchus is usually due to tuberculosis, although the latter process may have been combined in the node with silicosis. The transportation of stone dust to the liver and spleen occurs by way of the blood stream and results from the passage of dust into the small vessels of the lung, or from perforation of a vessel by a silicotic hilar node. In the spleen silicosis may lead to induration of the follicles similar to that of the bronchial nodes. Tuberculous induration of the bronchial nodes was found by Giese to be more frequent than the silicotic form. Silicotic induration of the bronchial nodes depends on the physical and chemical properties of the inhaled stone dust and may occur unassociated with silicosis of the lung.

O. T. SCHULTZ.

CONGENITAL ANOMALY OF THE HEART WITH TRANSPOSITION OF THE AORTA. L. KETTLER, Virchows Arch. f. path. Anat. **287**:10, 1932.

The heart, which is described in detail, came from a child that died at the age of 15 months. The clinical diagnosis during life had been congenital cardiac anomaly, with a surmise of defective ventricular septum and open ductus arteriosus. The auricular and ventricular septums were defective. There were three ventricular cavities. The third ventricle, which gave rise to a pulmonary artery with only two valve segments, had been formed by division of the right ventricle by the persistent septum of the bulbus arteriosus. There was no right auriculoventricular orifice; the left had five valve segments. The aorta arose from the right ventricle; the coronary arteries were transposed. The left superior cava was persistent; the right had disappeared. The pulmonary veins entered the heart by a single trunk. There was a persistent coronary sinus with two valves.

O. T. SCHULTZ.

SYNCYTIAL STRUCTURE OF GLIA. W. G. LAZAREW, Virchows Arch. f. path. Anat. **287**:227, 1932.

After reviewing the differences of opinion that have been held on the question whether normal glia has a syncytial structure or is composed of individualized cells, the author presents the results of a study of pathologic material derived from cerebral cysticercus, progressive paralysis and glioma of the brain. He concludes that in these conditions, at least, the glia has a syncytial structure. The nuclei of the syncytium have a limited degree of mobility.

O. T. SCHULTZ.

CYSTS OF THE POSTERIOR ROOTS OF THE SPINAL NERVES. U. HINRICHS, Virchows Arch. f. path. Anat. **287**:242, 1932.

As a chance observation at necropsy the author describes a pea-sized cyst situated at the point of union of the ganglion with the posterior root of three different spinal nerves. The patient was a woman, aged 61. The origin of the cysts could not be determined.

O. T. SCHULTZ.

HISTOLOGY OF HUMAN APOCRINE SWEAT GLANDS. W. RICHTER, Virchows Arch. f. path. Anat. **287**:277, 1932.

This study is based on a series of 106 autopsies in which the apocrine glands of the skin were subjected to a careful histologic examination as to their content of iron, fat and cholesterol. All of the apocrine glands examined were found to contain iron. Evidence is furnished that iron probably is excreted by the glands. Concerning the fat and cholesterol content, it was noted that while all apocrine glands excrete small amounts of fat and cholesterol, by far the most excretion takes place in the axillary glands. No difference was seen in the histology or secretory activity of the apocrine glands in the two sexes. During pregnancy regressive changes and diminished secretory activity of the axillary glands were observed. Pathologic processes occasionally were encountered, such as cystic dilatation, atrophy with connective tissue proliferation, hyaline and amyloid degeneration of the basal membrane and epithelial proliferation. In the ceruminal glands of the ear concretions were frequently observed.

W. SAPHIR.

CLASSIFICATION OF NEPHROSIS. W. EHRLICH, Virchows Arch. f. path. Anat. **287**:333, 1932.

In five of six cases of glomerulonephritis associated with amyloid nephrosis, hyaline and fatty degeneration of the tubular epithelium was found. These degenerative changes are due not to circulatory disturbances of the glomeruli but more likely, as the author points out, to a primary toxic influence. Hence they must be regarded as a complicating primary nephrosis. Lipoid degeneration of the tubular epithelium was noted in all of the cases examined. Based on previous studies and his own work, the author proposes the following classification of nephrosis: (*A*) tubular nephrosis: (1) primary—cloudy swelling, hyaline and fatty degeneration, necrosis; (2) secondary—fatty infiltration, hemoglobin infiltration, biliary infiltration; (3) combined (primary and secondary)—lipoid nephrosis; (*B*) glomerulonephrosis, with or without lipoid degeneration—amyloid nephrosis.

W. SAPHIR.

THYROID GLAND OF NORTH GERMAN AND SOUTH GERMAN RATS. W. ORYWALL, Virchows Arch. f. path. Anat. **287**:348, 1932.

Endemic goiter is confined to certain localities and in such areas affects domestic animals as well as the human population. As a preliminary to a proposed study of the biologic reactions of the thyroid, the author made a study of the thyroid of white rats of Stuttgart, an endemic goiter region of south Germany, and of rats from Leipzig, a nongoitrous district of north Germany. The thyroid of the

Stuttgart rat, both absolutely and relatively to body weight, is considerably heavier than that of the Leipzig rat. The thyroid of the south German rat has relatively less colloid and more epithelial tissue, to which its greater weight is attributed. The thyroid gland of the Stuttgart rats responded to small doses of iodine by a marked loss of weight. This was due to an increase in the colloid content and a corresponding decrease of epithelial tissue. The thyroid of Leipzig rats responded to small doses of iodine in a similar way but to a less marked degree. Larger doses of iodine caused marked epithelial hyperplasia. W. SAPHIR.

HISTOLOGY OF THE VALVULAR LESIONS OF ENDOCARDITIS LENTA. R. H. JAFFÉ, Virchows Arch. f. path. Anat. **287**:379, 1932.

Jaffé presents the results of a histologic study of the valvular lesions of six hearts selected from among thirty-five cases of typical endocarditis lenta (Schottmüller) or subacute bacterial endocarditis (Libman) that came to necropsy at the Cook County Hospital, Chicago. In all of the cases selected, Streptococcus viridans was isolated from the blood. The duration of the disease varied from six week to eleven months, and the age of the patients, from 21 to 56 years. Special attention was directed to the early stages of the lesion, which are often best seen in areas not macroscopically involved. Infection of the valves occurs by way of the blood flowing over the surface of the valves, and only rarely by way of the coronary arterial circulation. The localization of bacteria leads to swelling, proliferation and necrosis of the endocardium and to a proliferative mesenchymal reaction of the subendocardial stroma. If, at this early stage, the tissue reaction is successful in restraining the bacteria, none of the latter are seen in the lesion, and the lesion resembles the verrucous lesion of rheumatic infection. If the bacteria are able to multiply, they are seen first in giant cells of fibrocytic origin. These cells undergo necrosis, and the characteristic clumps of bacteria are seen at the surface of the vegetation. The tissue about the clumps may early undergo calcification. The vegetation is formed, not of thrombotic material that is deposited on the surface of the injured valve, but of granulation tissue that has grown outward from the valve and that readily undergoes fibrinoid degeneration and necrosis. This productive, necrotizing, granulomatous lesion is characteristic of subacute endocarditis. It remains for future study to determine whether the lesion is histologically specific of infection by Streptococcus viridans or whether it may also be caused by some of the other species of bacteria that have been isolated from clinically typical subacute bacterial endocarditis. Should the latter prove to be the case, the valvular lesion would then be the morphologic expression of bacterial allergy. O. T. SCHULTZ.

FIBROMYXOMATOUS HYPERPLASIA OF THE MITRAL VALVE. H. ENGEL, Virchows Arch. f. path. Anat. **287**:393, 1932.

A woman, 43 years of age, died suddenly with symptoms of cardiac failure. Necropsy revealed the mitral valve transformed into a polypoid, tumor-like formation of firm consistency. Histologically, the tumor was composed of fibromyxomatous connective tissue with numerous cell nuclei. In view of the absence of blood vessels and of inflammatory reaction, the author is inclined to classify the tumor in the group of endocardial tumors described by Ribbert, which are intermediate between hyperplasia and true blastoma. W. SAPHIR.

THE HEART IN DEATHS DUE TO EMBOLISM AND THROMBOSIS. I. PUTNOKY and K. FARKAS, Virchows Arch. f. path. Anat. **287**:400, 1932.

In a series of 1,009 necropsies, death was due to embolism in 9 per cent and to thrombosis in 6 per cent. In 52 per cent of the patients who died of embolism and in 60 per cent of those who died of thrombosis, pathologic changes of the heart were found. In the cases of embolism, the changes were as follows: chronic

endocarditis, in 36 per cent; arteriosclerosis, 29 per cent; syphilic aortitis, 17 per cent; acute endocarditis, 11 per cent, and myocardial fibrosis, 6 per cent. In the cases of thrombosis, the following cardiac conditions were found: arteriosclerosis, in 28 per cent; myocardial fibrosis and chronic endocarditis, 26 per cent, and acute endocarditis, 13 per cent.

W. SAPHIR.

VASCULAR CHANGES OF THE CENTRAL NERVOUS SYSTEM IN RHEUMATIC CHOREA. K. VON SÁNTHA, Virchows Arch. f. path. Anat. **287**:405, 1932.

In a girl, 15 years of age, who was suffering from chorea, complete muscular paralysis of all the extremities developed. She died sixteen days after the onset of the disease. Autopsy revealed, besides acute endocarditis and pneumonia, remarkable changes in the brain. The significant features were thrombosis, obliteration and recanalization of the small vessels of the pia mater. There were hyperemia, capillary endarteritis and small necrotic areas in the cortex and subcortex.

W. SAPHIR.

CARDIAC CHANGES IN DIPHTHERIA. DONNERSTAG, Virchows Arch. f. path. Anat. **287**:421, 1932.

The municipal hospital of Stettin has experienced an increasing number of deaths from diphtheria during recent years. The author reports the significant findings in a series of the fatal cases. In most of them death occurred with symptoms of cardiac failure shortly after the onset of the disease. Though gross cardiac changes were rarely noted, microscopically some or all of the following alterations were demonstrated in all cases: diffuse or circumscribed fatty degeneration, myolysis or hyaline degeneration of the muscle fibers, interstitial inflammation and connective tissue proliferation. The last two conditions were found only in the later stages of the disease.

W. SAPHIR.

CHANGES IN THE NERVOUS SYSTEM IN LEAD POISONING. H. FREIFELD, Virchows Arch. f. path. Anat. **287**:549, 1932.

Postmortem observations led the author to believe that there is no justifiable evidence for the assumption that lead is electively harmful to the nervous system. The harmful action is not due to a specific damage of ganglion cells, but is explained by the destructive action of lead on the blood vessels. Venous congestion and stasis interfere with the nutrition of nerve tissue and gradually lead to destruction of the tissue with the formation of glia. The genesis of lead colic is explained on the basis of degenerative changes of the solar plexus. Ingested lead is gradually absorbed by the impaired mucosa of the colon and taken up by the lymph, which carries it to the solar plexus. In the author's cases marked lymphangitis and dilatation of the lymph vessels of the retroperitoneal region were usually found.

W. SAPHIR.

EXTENSIVE NECROSIS OF THE INTESTINAL TRACT IN AGRANULOCYTOSIS. H. UFFENORDE, Virchows Arch. f. path. Anat. **287**:555, 1932.

In a case of agranulocytosis, the ulcerative lesions of the mucous membranes were not confined to the oral cavity, but were present in the entire alimentary tract from the oral cavity to the rectum. The most extensive changes were found in the esophagus, the mucous membrane of which was necrotic and separated entirely from the muscularis. The author presents a brief summary of the bibliography. Of 317 cases of agranulocytosis reported in the literature, the author believes that only 248 can be considered as true cases of agranulocytosis. Of these, there are only 40 (16 per cent) which offer proof for the assumption of an infectious etiology. In 37 cases the relation of preceding infection to the onset of the disease

seems doubtful. For the majority of the cases of agranulocytosis reported in the literature, the author considers as the most satisfactory explanation the assumption of an impaired myeloid system due to either congenital or acquired factors of various origin.

W. SAPHIR.

CHANGES IN THE OSSEOUS CAPSULE OF THE INTERNAL EAR IN RELATION TO THE HISTOPATHOLOGY OF THE SKELETAL SYSTEM. M. MEYER, Virchows Arch. f. path. Anat. **288**:1, 1933.

This is one of four articles on the pathology of the osseous system that occupy the first 211 pages of a number of *Virchows Archiv für pathologische Anatomie und Physiologie und für klinische Medizin*. Meyer's contribution, which interprets a variety of pathologic states of the skeletal system in the light of changes observed in the bony capsule of the internal ear, is based on the recent monograph of Nager and himself. In the skeleton under normal conditions, bone is constantly being resorbed and reformed; the skeleton is being continuously rebuilt. In diseases characterized by abnormal bone resorption or bone formation, what actually occurs may be difficult to determine because it is not always easy to distinguish between the normal and the abnormal processes. The development of the labyrinthine capsule is completed by the end of the second year of life. Thereafter no changes occur under normal conditions. Furthermore, the bone of the capsule has a different structure than that of the bone of the rest of the skeleton. It consists of islands of calcified embryonic cartilage embedded in compact bone that is fibrillated and not laminated like other compact bone. If the capsule participates in systemic skeletal diseases, the early completion of development and the different structure should aid in the interpretation of the general diseases, since resorption and new formation of bone can be readily detected and the newly formed bone is laminated bone and not the normal fibrillated bone. Pommer has claimed that in senile osteoporosis bone resorption is normal, but reformation of bone is deficient. According to Meyer, examination of the capsule of the internal ear establishes that new bone formation is very slight, but resorption of bone is marked. The moot question as to whether osteomalacia is primarily a regressive process Meyer answers by saying that the uncalcified bone is not original bone that has undergone regressive changes but is newly formed, uncalcified, laminated osteoid tissue that has been laid down on the trabeculae of the original fibrillated bone. He could detect no evidence of halisteresis in the labyrinthine capsule in osteomalacia. He agrees with Schmorl, Schmidt and others that rickets is essentially the same process as osteomalacia but differs in its effects because rickets occurs at an age when bone formation is active. In rickets little change was noted in the inner, enchondral portion of the capsule. But in the outer, perichondrial portion, the formation of osteoid tissue was so great and characteristic as to permit the histologic diagnosis of rickets. Fibrosis of the marrow is not the primary factor, but is secondary to the bony changes. Fibrosis of the marrow leads to deficient pneumatization of the mastoid. In osteodystrophia fibrosa, which includes Recklinghausen's disease and Paget's disease, the capsule of the internal ear reveals a characteristic mosaic structure identical with that of other bones. Osteoclastic resorption of the original bone is followed by the formation of immature bone, which becomes transformed into mature fibrillated bone. About the marrow spaces laminated bone is deposited. The mosaic pattern is due to the intermingling of the different kinds of bone in varying stages of maturity. The changes in the bony capsule of the internal ear were identical in Recklinghausen's disease and Paget's disease. More attention is paid to otosclerosis than to any other subdivision of the article. The changes in the bony capsule are identical with those of osteodystrophia fibrosa, of which disease otosclerosis is considered a form limited to the petrous bone. Identical histopathology does not necessarily presuppose a similar etiology. In endemic cretinism, the chief change in the temporal bone is hyperplasia and hypertrophy of the subperiosteal bone; the enchondral and perichondrial portions of the capsule of the internal ear reveal only slight change. In mongolian idiocy no changes were noted,

a fact that speaks against a postulated relation of mongolism to cretinism. Congenital osteogenesis imperfecta is characterized not only by disturbed osteoblastic function of the bone, but by a widespread disturbance of the mesenchyme. In chondrodystrophy, the cartilage of the labyrinthine capsule is invaded by strands of connective tissue carrying blood vessels.

O. T. SCHULTZ.

LYMPHOGRANULOMATOSIS OF BONE. E. UEHLINGER, Virchows Arch. f. path. Anat. **288**:36, 1933.

This report is based on the study of fifty cases of lymphogranulomatosis, in forty-eight of which the diagnosis was established by necropsy and in two by biopsy. The age of the patients varied from 12 to 77 years. Sixteen died in the third decade and twelve in the fourth. Twenty-three of the patients were males and twenty-seven females. Lymphogranulomatosis is a specific infection, which is histologically distinct from tuberculosis and lymphosarcoma. Primary involvement of bone or involvement limited to bone does not occur. Lymphogranulomatosis of the skeleton is a secondary process and arises either by direct continuity from a contiguous focus or by hematogenous metastasis. In Uehlinger's series, invasion of bone by direct continuity occurred twelve times and metastatic involvement five times. Under the metastatic cases Uehlinger includes only those in which the skeletal involvement was so widespread as to influence the clinical course of the disease. Direct erosive invasion occurred most often in the vertebrae, next in the sternum and pelvis and least often in the ribs, clavicle and scapula. The process begins in the periosteum, penetrates the lacunae of the cortex and spreads in the marrow, which is pushed aside or replaced. In the gross the process cannot be distinguished from an invasive neoplasm. The roentgenologic picture is not characteristic. Invasion of bone is usually painless and generally occurs relatively late in the course of the disease. Invasion of bone by direct continuity led to no characteristic or striking changes in the blood in Uehlinger's cases. In the marrow histologically specific tissue is formed; this tissue quickly undergoes fibrosis, even in the absence of irradiation therapy. The bone undergoes osteolysis and osteoporosis. The formation of endosteal and periosteal bone was infrequent. The radiosensitivity of the tissue varied and appeared to depend on the duration of the disease as a whole. The distribution of the lesions in hematogenous skeletal involvement coincided with the distribution of red marrow in the adult. The process begins as specific osteomyelitis, which leads to replacement and fibrosis of the marrow. Clinically, such cases were characterized by progressive anemia and leukopenia. The bone itself revealed relatively little change, and the roentgenologic findings were indefinite. The vertebrae, sternum and head of the femur were most often involved, the ribs, pelvis and cranium less often. Metastatic skeletal involvement occurred early in the course of the disease, which ran a rapidly progressive course.

O. T. SCHULTZ.

RENAL DWARFISM AND RENAL RICKETS. H. HAMPERL and K. WALLIS, Virchows Arch. f. path. Anat. **288**:119, 1933.

A detailed clinical and pathologic study of two cases of dwarfism is presented. Both patients were girls, aged 11 years and 3 months and 10 years and 5 months, respectively. The first had the stature of a girl of 6 years and 10 months, the second that of a girl of 5 years and 4 months. The body proportions were normal. The clinical findings were those of chronic interstitial nephritis, for whose onset no cause could be discerned in the history. The presence of chronic interstitial nephritis, with small contracted kidneys, was confirmed at necropsy. In the older girl, changes in the bones were very slight and were limited to the costochondral junctions of the ribs. The alterations were such as are seen in the ribs in very mild rickets. In the younger child, the roentgenologic and the histologic findings were those of marked rickets. The authors do not believe that the nephritis

was the direct cause of either the dwarfism or the rickets. If any important rôle is to be ascribed to the nephritis, it seems necessary to assume that the renal factor acts on a special constitutional factor. The authors prefer to assume that the same noxa caused the nephritis, the infantilism and the rickets.

O. T. SCHULTZ.

SYPHILIS OF BONE. E. FREUND, Virchows Arch. f. path. Anat. **288**:146, 1933.

Most of the literature of syphilis of the bone dates from a period when the histopathology of bone was not so well known. Freund's study, carried out in Erdheim's institute, is based on a study of the bones in five cases of late syphilis. The process begins as a gummatous osteomyelitis or as a syphilitic periosteitis, the agent reaching the tissues by way of terminal vessels, about which the first changes occur. Diffuse osteomyelitis occurs, but is rare. Diffuse productive periosteitis is more common, but the periosteal lesions may also be gummatous. Caseation may be followed by softening and removal of the necrotic material by phagocytic histiocytes, giant cells and leukocytes. If the removal is complete, the gumma is replaced by dense fibrous tissue. If the necrotic material is incompletely removed, it becomes encapsulated and may undergo calcification. As the inflammatory tissue invades the spongy bone, the latter may undergo lacunar resorption, leading to the formation of spaces into which the syphilitic tissue grows. If the invasion of bone is more rapid, the bone undergoes caseous necrosis. Porosis and sclerosis of bone occur about the gummas. Microfractures of the bony trabeculae are not uncommon. Larger fractures may lead to nearthroses. Healing may lead to a restitution of the osseous tissue to normal, to complete replacement of the shaft of a long bone or to the bony encapsulation of defects caused by necrosis.

O. T. SCHULTZ.

UNUSUAL ANOMALY OF THE FACE IN AN ANENCEPHALIC MONSTER. B. RATING, Virchows Arch. f. path. Anat. **288**:223, 1933.

In an anencephalic monster 32 cm. in length, an accessory nose was situated between a double right eye and the root of the normal median nose. The upper lip, palate and maxilla were cleft. The maldevelopment is made the basis of a discussion of incomplete reduplication anomalies of the face.

O. T. SCHULTZ.

CONGENITAL ATRESIA OF THE LARYNX WITH HYPERTROPHY OF THE LUNGS AND GENERALIZED HYDROPS. A. KOVÁCS, Virchows Arch. f. path. Anat. **288**:243, 1933.

In a female infant weighing 2,500 Gm., respiratory movements and contractions of the heart continued for twenty minutes after birth. The body was markedly edematous, and the peritoneal cavity was filled with fluid. Necropsy revealed complete atresia of the larynx and marked enlargement of the lungs. Other anomalies were absence of one kidney, ovary and oviduct; atresia of the anus and vagina, and ankyloblepharon. The increase in the size of the lungs was due to distention of the alveoli by mucus. The pulmonary hypertrophy and the hydrops were the direct results of the atresia of the larynx, which interfered with the escape of mucus from the bronchial system. Hydrops was the result of mechanical compression of the heart and vessels by the distended lungs. According to the author, only seven examples of congenital atresia of the larynx have been previously reported. In one of these the lungs were enlarged and there was hydrops. In other cases the state of the lungs was not noted. The author thinks that the enlargement was overlooked, since hydrops was present in several cases.

O. T. SCHULTZ.

ACCESSORY TONGUE. K. M. MENZEL, Virchows Arch. f. path. Anat. **288**:253, 1933.

Anomalies previously described as accessory tongue have been rounded masses in the floor of the mouth that contained cartilage or adipose tissue and that were attached to the body of the hyoid bone or to the septum of the tongue. They have had little structural resemblance to the normal tongue. Menzel carefully describes as accessory tongue two examples of a congenital anomaly that he claims has never been heretofore recorded. One was in a youth, aged 16, the other in a woman, aged 26. In each instance the accessory tongue was about the size of a walnut. It exhibited spontaneous fibrillary and coarser contractions and had a papillary surface like that of the base of the tongue. In the boy the mass was attached to the lower pole of the left tonsil. In the woman it was attached to the right side of the base of the tongue; the right tonsil and faucial pillars were absent. In each case the anomaly was associated with atresia of the external auditory canal, absence or maldevelopment of the external ear, maldevelopment of the middle ear and congenital paresis of the facial nerve, in each case on the same side as the lingual anomaly. The internal ear and labyrinth were functionally normal. Taste sensation of the accessory tongue of the boy was carefully tested and was found to be present and normal. Histologic examination of the structure after removal showed it to have a surface like that of the normal tongue, with filiform and circumvallate papillae and taste buds. The deeper portion of the mass consisted of striped muscle. Atresia auris associated with paresis of the facial nerve has frequently been described. These conditions are ascribed to defective development arising not later than the third fetal month in the region of the first and second branchial arches. Menzel believes that the accessory tongue described by him arose from multipotent tissue of this same region.

O. T. SCHULTZ.

ANOMALIES OF THE MÜLLERIAN DUCT. C. O. KESSELBURG, Virchows Arch. f. path. Anat. **288**:269, 1933.

Defective development of the derivatives of the müllerian duct is usually associated with cloacal defects. In the two fetuses described, the rectum and bladder were normal. In one, a rudimentary left uterus, to which a normal tube and ovary were attached, was connected with the bladder by a narrow duct whose opening into the bladder was situated beside the ureter of the same side. The urinary tract and a separate right uterus, tube and ovary were normal. In the second case there was complete duplication of the uterus. The left uterus, to which a tube and ovary were attached, opened into a normal vagina. The right uterus opened into a short, rudimentary vagina which communicated with the urethra and the left vagina. The right kidney, ureter, tube and ovary were absent.

O. T. SCHULTZ.

RELATION OF ALTERATIONS IN THE BRAIN TO HEPATIC DISEASE. H. J. SCHERER, Virchows Arch. f. path. Anat. **288**:333, 1933.

The constant occurrence of cirrhosis of the liver in Wilson's disease led to the histologic examination of the brain in forty-one cases of various kinds of hepatic disease. In addition to ordinary atrophic cirrhosis and acute yellow atrophy, the series included cases of pigmentary cirrhosis, fatty cirrhosis, widespread primary and secondary carcinoma of the liver and pseudocirrhosis of marked passive congestion. Changes in the macroglia were noted in 90 per cent of all the brains examined. These changes consisted in the presence of an increased number of enlarged, vesicular, naked nuclei. This process was independent of any parenchymatous changes in the brain. A probable histologic diagnosis of disease of the liver is possible from these cerebral changes. The degenerative changes of the ganglion cells of the basal ganglions, characteristic of Wilson's disease, were not observed in any instance in this series. The glial reaction of Wilson's disease is held to be secondary to the coexisting disease of the liver.

O. T. SCHULTZ.

CHANGES IN THE MUSCLES AND NERVES IN PARALYSIS AGITANS. ELSE PETRI, Virchows Arch. f. path. Anat. **288**:370, 1933.

Degenerative, regressive changes were noted in the brachial plexus and in the nerves of the forearm and in the muscles of the forearm, pharynx and tongue in a case of paralysis agitans which revealed relatively slight alterations in the central nervous system. The author suggests that death in this disease may be due to involvement of the diaphragm. O. T. SCHULTZ.

CONTRACTED KIDNEY DUE TO SCLEROSIS OF THE MEDULLA. K. HELPAP, Virchows Arch. f. path. Anat. **288**:383, 1933.

The kidneys of 126 elderly persons were examined with reference to the degree of renal arteriosclerosis and the extent of fat and calcium infiltration of the medulla. No direct relationship between the two processes was found to exist. With the point of view of the independence of arteriosclerosis and medullary intertubular change as a background, the author describes four examples of marked fibrosis of the medulla which was associated with changes in the cortex and with relatively slight arteriosclerosis. The glomeruli were only slightly altered. The cortical involvement is held to be secondary to the medullary sclerosis and is likened to that of the hydronephrotic contracted kidney. Localized fatty infiltration and calcification of the medulla with tubular atrophy may lead to localized ascending sclerosis of the cortex. A combination of medullary sclerosis and arteriosclerosis may lead to the most extreme degree of renal contraction. O. T. SCHULTZ.

Immunology

QUANTITATIVE PRECIPITIN STUDY ON RABBITS INJECTED WITH AN AZO PROTEIN. M. HEIDELBERGER, F. E. KENDALL and C. M. SOO HOO, J. Exper. Med. **58**:137, 1933.

The preparation of a deep red protein dye, R-salt-azobenzidine-azocrystalline egg albumin is described, which contains no more than traces of protein with the original specificity of egg albumin. Based on previous publications of the authors, a method is given for the microscopic quantitative estimation of precipitin in antiserums to the dye. The method gives the actual weight of the precipitin and may be applied to the determination of the maximum amount of precipitable antibody in any antiserum. Data are given (1) on the influence of the period between the final injection and the bleeding on the precipitin content of rabbit antiserums to the azoprotein; (2) on the magnitude of the antibody response following the injection of multiple doses of the antigen varying within wide limits; (3) on the variations in the precipitin content of the serums of rabbits given successive courses of injections of the antigen, and (4) on the stability of the antiserums in cold storage. Four antiserums were obtained from which the amount of precipitin recovered was over one hundred times the amount of antigen injected. This supplements the growing mass of evidence against the theory that fragments of specific antigen are incorporated in the antibody molecule. AUTHOR'S SUMMARY.

IMMUNIZATION WITH PURIFIED HAPTENS. H. MERCKENS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:308, 1933.

The purification of alcoholic extracts of organs, according to Weil and Ritzenthaler, is based on removal of the lecithin and cephalin compounds with cadmium chloride and subsequent precipitation with acetone. Immune serums of rabbits treated with mixtures of such extracts and diluted hog serum possessed all the qualities of the serums produced with unmodified extracts. I. DAVIDSOHN.

ADSORPTION AND ELUTION OF THE ANTIGENIC SUBSTANCE. A. J. WEIL, B. RITZENTHALER and H. MERCKENS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:316, 1933.

The antigenic substance can be removed from alcoholic extracts by adsorption with kaolin and other inorganic adsorbing compounds, and it can then be liberated by washing with water, physiologic solution of sodium chloride, alcohol or methyl alcohol, but not with acetone or ether. The adsorption is equally easy from acetone extracts, but the subsequent elution is not possible. The antigens which were purified according to the procedure of Weil and Ritzenthaler behaved in the same manner with regard to adsorption and elution as did the nonpurified extracts.

I. DAVIDSOHN.

MECHANISM OF THE FORMATION OF ANATOXIN. S. SCHMIDT, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:339, 1933.

The article contains a review of the hypotheses by which authors have attempted to explain the nature of the detoxifying process. After a critical analysis of the available facts, Schmidt concludes that no satisfactory and fool-proof explanation has been advanced. The facts available are that the marked chemical and thermal resistance, the irreversibility of the detoxifying process and the drop of the amino-nitrogen values differentiate the anatoxin from the toxoid. Purified toxins are readily changed into anatoxins.

I. DAVIDSOHN.

TRANSFERABLE AND INHIBITING SUBSTANCES IN THE BLOOD OF ALLERGIC PATIENTS. W. KREMER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:382, 1933.

The transferable substances (allergens) were determined by means of the method of passive transfer, and the inhibiting substances (antiallergens) were demonstrated by mixing the allergens with the patient's blood or blood serum and then injecting the mixture intracutaneously. The usual cutaneous reaction was inhibited in the presence of antiallergens. Both types of substances are found frequently, but they need not be present simultaneously, as was seen in three patients who had only one kind of substance in the blood. Both types of substances always correspond with the allergens to which the patient is sensitive. They were never found in nonallergic persons. The antiallergens are transferable to the skin of other persons sensitive to the same allergens. The author concludes that the transferable allergens and the antiallergens are not identical.

I. DAVIDSOHN.

BOILED LIQUID SERUM AS ANTIGEN FOR THE PREPARATION OF PRECIPITATING ANTISERUMS. F. P. LEUSDEN and ERWIN PETRICH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:393, 1933.

Serums of the sheep, goat, ox, horse and pig and that of man were diluted with distilled water, boiled and used for immunization of rabbits. The precipitin titers for the homologous antigens and for the unheated serums were determined on several occasions during the treatment. The titers for the homologous antigens rose early, though only moderately, but soon became stationary, while those for the unheated serums rose slowly, reached a higher peak than the former and then dropped rapidly. Differentiation of the unheated and the boiled serum by means of precipitins produced with the boiled serum was not possible. Group reactions were observed with native and with boiled serums, while nonspecific reactions occurred only with boiled serums.

I. DAVIDSOHN.

INFLUENCE OF VENESECTION ON THE TITER OF DIPHTHERIA ANTITOXIN. E. F. GOGIN and E. G. ZURINOWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:404, 1933.

The titer of the immune serum of horses was determined by means of the flocculation test of Glenny and Okell. The titer was highest eight days after the last injection of the antigen and dropped steadily afterward. The variations in

the titer could not be correlated with any known factors. The bleeding of the horses on the eighth and tenth days proved most satisfactory; an additional third bleeding is not advisable. The amount of serum obtained at the second bleeding was from 7 to 8 per cent larger than that obtained at the first.

I. DAVIDSOHN.

COMPARATIVE STUDIES OF THE PURIFIED TOXINS OF STREPTOCOCCI OF SCARLET FEVER AND OF ERYSIPELAS. W. A. KRESTOWNIKOWA and E. M. RJACHINA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:414, 1933.

The strains Dick 8 and Dochez were used for the preparation of the toxin of scarlet fever streptococci, and the strain Birkhaug 4c was the source of the erysipelas toxin. The purification consisted of removal of proteins, dialysis, inspissation, precipitation with alcohol and drying. The final product, a powder, was insoluble in lipoid solvents and contained a carbohydrate substance. The two toxins differed in quantitative chemical composition; the difference became more or less obliterated with the progress of purification. Both products were toxic when injected intracutaneously, the toxicity of the scarlet fever streptococcus being very much more marked. Characteristic cutaneous and systemic changes were studied, the latter occurring only after intravenous introduction of the toxin of the scarlet fever streptococcus. Continued dialyzing lowered the toxicity of the toxin of scarlet fever to the level of that of the erysipelas toxin. Immune serum introduced one or two days previous to the intracutaneous injection prevented the appearance of the cutaneous manifestations. The toxin gave positive precipitation and complement-fixation reactions with immune serums. The antigenic action of the toxin of the scarlet fever streptococcus was much more pronounced than that of the erysipelas toxin. Potent immune serums were produced in rabbits treated with the purified toxins. The toxins possess all the qualities of full antigens.

I. DAVIDSOHN.

THE BEHAVIOR OF BRAIN EXTRACTS IN SEROLOGIC REACTIONS. GERTRUD PRÜSSE, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:437, 1933.

The purpose of this investigation was to determine whether the frequently observed positive complement-fixation reactions between alcoholic extracts of brain and cerebrospinal fluid are specific or whether they are due to the composition of the fluid. The latter assumption was found to be true, because the fixation did not take place when normal human serum was added to the cerebrospinal fluid. The positive reaction of the fluid with the regular heart extract was only occasionally slightly weakened by the addition of normal serum. Not all human serums had the ability to modify the reaction of the cerebrospinal fluid. The reaction with brain extract of an antiserum against beef heart extract was similarly removed after the addition of normal serum. The addition of normal rabbit serum had a similar effect on the reaction between a heterophilic immune serum and a weak Forssman antigen, but the reaction with a strong antigenic extract was not influenced.

The author concludes: If cerebrospinal fluid giving a positive Wassermann reaction reacts with brain extracts and the blood serum does not react, the phenomenon is due not to the presence of specific brain antibodies in the fluid but to colloidal differences between cerebrospinal fluid and blood serum.

I. DAVIDSOHN.

MENINGOCOCCUS TOXIN. W. KRESTOWNIKOWA, A. BELKINA, E. DOSSER and I. LASOWSKY, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:451, 1933.

Cultures of A, B and C strains of meningococci developed, after from five to six days, a toxic filtrable substance which was characterized by marked thermostability (it stood boiling for fifteen minutes) and by resistance to freezing and thawing. The toxin could be concentrated by Huntoon's method. It was

toxic to mice, rabbits and guinea-pigs. Animals killed by intraperitoneal injections showed at postmortem examination pronounced toxic-degenerative, but nonspecific, changes. The changes in rabbits dying of meningitis after suboccipital introduction of the filtrate were similar to those which follow meningitis produced by bacteria. The filtrates reacted with immune and convalescent serums in the form of flocculation, precipitation and complement fixation. Mixing of bacterial immune serums with the filtrate protected mice, which shows that bacterial immune serums contain antitoxin. Formaldehyde detoxified the filtrate. Rabbits inoculated with the filtrate produced precipitating and complement-fixing immune serums. The toxic substance in the filtrates resembles the toxin of the scarlet fever streptococcus. It is a polysaccharid; it produces similar intracutaneous lesions in man and shows other similar features.

I. DAVIDSOHN.

SEROLOGIC SPECIFICITY OF THE SUPRARENAL MEDULLA. E. WITEBSKY and J. KLINKE, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:509, 1933.

The serum of rabbits treated with suspensions of carefully separated medullary parenchyma of the suprarenal glands of oxen reacted in complement-fixation tests specifically with alcoholic extracts and less strongly with aqueous suspensions of suprarenal medulla of the ox, the hog and the sheep. Some antiserums reacted slightly with suprarenal cortex, but the impression was gained that whenever the material which was used for immunization had been thoroughly freed from cortical parenchyma the organ specificity of the antiserum was absolute. Brain antiserums reacted with extracts of suprarenal medulla, which is explained by the embryologic relations of both organs; however, antiserums against suprarenal medulla failed to react with brain extracts. The results of this investigation increase the number of organs which are known to produce organ-specific immune serums to five (the lens, brain, spinal cord, posterior lobe of the hypophysis and suprarenal medulla).

I. DAVIDSOHN.

PROPHYLACTIC VACCINATION IN ICTEROHEMORRHAGIC SPIROCHETOSIS. HIDETSUNE WANI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:1, 1933.

The spirochetes were grown in pure culture on a modification of Noguchi's ascitic fluid-kidney-paraffin medium. Inada and Ido are the authors of the modification. The vaccine was injected in two doses of 2 and 3 cc. between the shoulder blades. The vaccination was carried out on 10,268 miners who were employed in Japanese coal mines known to have been infested with the disease for many years. Only 0.13 per cent of those vaccinated contracted the disease, while among the untreated persons 1.12 per cent became infected. An epidemic in one of the mines was quickly terminated by vaccination of all miners. The immunity acquired by vaccination was present nineteen months after the treatment. The symptoms resulting from the vaccination were insignificant. The most serious complication was occasional formation of abscesses on the site of injection. An appendix contains a review of 14,686 vaccinations which were carried out by Majima in different groups of miners. The results were satisfactory.

I. DAVIDSOHN.

ADSORPTION OF ALCOHOLIC EXTRACTS OF ORGANS. TRUDE FISCHER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:39, 1933.

The article confirms the reports of various investigators that the haptens can be removed from alcoholic extracts of organs by means of various adsorbents. Cholesterolized alcoholic extracts of beef heart were deprived of their ability to fix complement in the presence of syphilitic serums after adsorption with barium sulphate and with calcium phosphate, but not after adsorption with aluminum hydroxide and kaolin. Such adsorbed extracts reacted with lipoid antiserum of rabbits. The heterophilic antigenic substance was removed both from undiluted and from diluted alcoholic extracts of horse kidney with specially prepared kaolin.

The kaolin was then able to react with a heterophilic immune serum. The antigenic substance could be removed from kaolin and calcium phosphate by treating them with alcohol, but treatment with distilled water and salt solution was not suitable for that purpose.

I. DAVIDSOHN.

SEPARATION OF LIPOID HAPTENS WITH INORGANIC COMPOUNDS. A. KLOPSTOCK and T. MISAWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:53, 1933.

The different haptens contained in alcoholic extracts of organs react differently with various adsorbing compounds. The investigation included the so-called lecithin hapten, which is present in all tissues and which reacts with serums produced in rabbits inoculated with commercial lecithin. Kaolin, aluminum hydroxide and calcium phosphate were not able to adsorb the lecithin hapten from alcoholic extracts of organs, but did absorb it from alcoholic solutions of commercial lecithin. The Wassermann lipoid hapten appeared to be adsorbed from alcoholic extracts of heart when they were tested with human syphilitic serums, but the same extracts retained some ability to react with rabbit immune serums. The A group-specific hapten was removed by aluminum hydroxide and calcium phosphate from alcoholic extracts of organs and of blood; the species-specific hapten could not be removed. The ability of the organ extracts and of lecithin to activate the hemolytic ability of cobra poison was removed by treatment with kaolin, but the other compounds had little or no effect.

I. DAVIDSOHN.

IMMUNIZING ABILITY OF THE ADSORBED HETEROPHILIC HAPTEN. T. MISAWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:80, 1933.

The report deals with another attempt to throw light on the significance of the nonspecific protein which is necessary for successful immunization with the specific lipoid hapten. The conception of Sachs, Klopstock and Weil that the protein is only an adjunct acting as a carrier would be supported if immunization were possible without admixture of an antigenic substance. Armangué and his associates claimed to have accomplished it by using kaolin, animal charcoal and other nonantigenic substances. Misawa failed to obtain an antibody response in rabbits treated with a mixture of an alcoholic extract of horse kidney with kaolin. A slight response was observed when animal charcoal was used as an admixture, but that result lost its significance when a rabbit which was inoculated with the charcoal only showed heterophilic antibodies. There may have been a connection between the peculiar antibody response and an infection of the inoculated animals with Bacillus lepisepticus, some strains of which have been shown to contain heterophilic antigen. The attempt to employ collodium as the complementary antigenic admixture to the alcoholic extract of horse kidney failed, though in test tube experiments the collodium adsorbed completely the Forssman antigen from the alcoholic extract.

I. DAVIDSOHN.

LOCAL ANAPHYLAXIS OF DIFFERENT ORGANS. HANS SCHOLER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:99, 1933.

Rabbits were treated with subcutaneous injections of horse serum till they reacted with an Arthus phenomenon. The injection of horse serum into the wall of the small intestine or into the mesentery produced no inflammatory reactions, while distinct local reactions were noted when the injection was given into the wall of the stomach. The reaction consisted in edema, vascular stasis, perivascular leukocytic infiltration and early necrosis. No such reactions occurred following reinoculation with a heterologous serum. The results confirm the observations of Shapiro and Ivy in regard to the particular local sensitiveness of the gastric wall. The lack of reactivity on the part of the intestinal wall is not due to its inability to respond to local irritants.

I. DAVIDSOHN.

TITER AND CONCENTRATION OF PRECIPITINS. TAKEO SATOH, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:117, 1933.

The titer of precipitins in an immune serum is a distinct and separate quality from their concentration. The concentration of the precipitins determines the content of the serum. The latter is determined by using the opposite procedure from that employed in the estimation of the titer: The immune serum is diluted and the antigen remains constant. Rabbits showed a high precipitin titer after a single injection, but the concentration of the antibodies was low; after repeated injections the concentration increased, while, as a rule, the titer remained approximately unchanged. The heterologous nonspecific precipitins were almost absent following a single injection; following multiple injections their titers were so high that the specific character of the serums was almost lost. The concentration of the heterologous precipitins was low, and the specific nature of the serum could be demonstrated by proper dilution with normal rabbit serum. The coarseness of the precipitate was greater in serums with a higher concentration of the antibody, but was not dependent on the titer. Resistance to heat, to chemicals and to physical influences and the complement-fixing ability of the immune serum were also dependent on the concentration of the precipitins, but not on the height of their titer.

I. DAVIDSOHN.

STANDARDIZATION OF ANTITOXIC STAPHYLOCOCCUS SERUM. H. GROSS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:163, 1933.

The hemolytic, the necrotizing and the systemic toxic qualities of the staphylococcus toxin are met by the corresponding antibody manifestations in the immune serums produced by treatment of rabbits with filtrates of from two to three week old broth cultures of strongly hemolytic and highly toxic staphylococci. Gross suggests the employment of the antihemolytic titer as an index of the antitoxic value of the immune serums. One-one hundredth cubic centimeter of a serum able to inhibit the minimal hemolytic dose of the toxin should be agreed on as the unit of antitoxin. The minimal hemolytic dose is the smallest amount of toxin which hemolyzes 1 cc. of a 1 per cent suspension of rabbit red blood cells after one hour of incubation at 37 C.

I. DAVIDSOHN.

ANTAGONISM BETWEEN RED BLOOD CELLS AND ORGANS OF THE RABBIT IN CONTENT OF A SUBSTANCE. WALTER TREIBMANN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:274, 1933.

The failure of rabbits without normal anti-A agglutinins to produce group-specific anti-A serums is due to the presence of the A quality in their tissues and blood serum. This was demonstrated by Treibmann by means of the inhibiting effect of such tissues on the hemolysis of sheep red cells by immune serums produced with human group A red cells. The procedure of the inhibition of hemolysis, as suggested by Brahn and Schiff, proved the most sensitive of all methods for the demonstration of the quality A. Complement fixation with watery suspensions and with alcoholic extracts was also employed. The substance A could not be demonstrated in the red blood cells of rabbits which had varying quantities of it in the other tissues. Rabbits with normal anti-A agglutinins in their serum do not possess the A quality in their tissues.

I. DAVIDSOHN.

ANALYSIS OF BLOOD ANTIGENS WITH THE HELP OF HETERO-AGGLUTININS. M. EISLER and A. HOWARD, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:293, 1933.

The effect of red blood cells of different species of animals on normal hetero-agglutinins in their serums permitted the recognition of identical antigenic substances in the blood cells of distant species and of differences in the blood cells of closely related species and of individuals of the same species. The results con-

firmed those obtained by various authors in the study of immune serums against various bloods. The distribution of the common antigenic substances shows no apparent relation to the zoological system. Witte's peptone inhibited the agglutination of certain red blood cells by some normal serums. The inhibiting effect of the peptone was removed by fecal extracts.

I. DAVIDSOHN.

PRODUCTION OF ANTIBODIES AGAINST CARBOHYDRATES (ACACIA). P. UHLENHUTH and E. REMY, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:318, 1933.

As far back as 1904, Uhlenhuth reported flocculation in a mixture of a suspension of acacia with normal serum of some animals. In rabbit serum which did not react with flocculation normally, flocculation occurred after immunization with acacia. The in vitro reaction also took place with arabic acid and with its calcium salt. Uhlenhuth in the original publication emphasized the significance of the observation, which suggested antigenic qualities of a carbohydrate substance, but reserved a definite opinion till arabic acid should be produced in a chemically pure state. The experiments were recently successfully repeated with the cooperation of Remy. The production of antibodies was demonstrated by means of the precipitation and complement-fixation reactions. The failure to obtain a nitrogen-free arabic acid again prohibited definite chemical conclusions as to the antigenic rôle of the carbohydrate in acacia.

I. DAVIDSOHN.

SEROLOGIC SPECIFICITY OF THE PINEAL GLAND. E. WITEBSKY and H. REICHNER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:335, 1933.

Relative and quantitatively limited serologic specificity of the pineal gland could be demonstrated by means of immune serums produced in rabbits with aqueous suspensions of the organs, while immune serums produced with alcoholic extracts did not permit differentiation from the brain. Differentiation from other organs than the brain was accomplished. The organ-specific quality is therefore insoluble in alcohol and thermolabile.

I. DAVIDSOHN.

BEHAVIOR OF COMPLEMENT AND OF ITS COMPONENTS DURING ADSORPTION AND ELUTION. LEO OLITZKI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:347, 1933.

For adsorption, kaolin, aluminum hydroxide and a compound, *silargèle* (the nature of which is not mentioned), were used. The attempts to liberate the adsorbed active substance by washing with various solutions (glycine and sodium chloride, glycine and sodium hydroxide, sodium phosphate and glycerin) were not successful when the whole complement was adsorbed, but some of the active principle was freed when the separated midportion was used. The end-portion of the complement had a greater activating ability than the midportion.

I. DAVIDSOHN.

THE CONTENT OF AGGLUTININS IN COMBINED ORAL AND SUBCUTANEOUS TYPHOID IMMUNIZATION. HEINRICH RUGE, Zentralbl. f. Bakt. (Abt. 1) **124**:276, 1932.

Twenty-two men were given a lysate of typhoid bacilli by mouth and four weeks later were immunized subcutaneously with the same type of lysate. Agglutination tests made four weeks after the oral administration of the lysate were positive in two thirds of the subjects. Following subcutaneous vaccination the tests showed higher titers in those who had previously given positive reactions after oral immunization than in those who had received the lysate only subcutaneously. The author concludes that oral immunization favors the formation of agglutinins.

PAUL R. CANNON.

Tumors

GLIOMA OF THE CEREBRAL HEMISPHERES. H. BERGSTRAND, Virchows Arch. f. path. Anat. **287**:797, 1933.

The author examined about one hundred cerebral gliomas. One third of them were clinically benign, and two thirds were clinically malignant. Following a detailed description of the specimens, the author considers Cushing and Bailey's classification too artificial and furthermore unnecessary. He proposes a subdivision into benign astrocytoma and malignant glioblastoma. At times, however, it may be impossible to draw a sharp line between these two forms.

W. SAPHIR.

MORPHOLOGY OF GLIOMA. L. SINGER and J. SEILER, Virchows Arch. f. path. Anat. **287**:823, 1933.

The authors' studies lead them to conclude that the astrocytic glia of the glioma must be differentiated from the tumor parenchyma. The astrocytic glia and the mesodermal reticulum constitute the stroma of the growth. The tumor tissue itself is held to originate in differentiated nerve cells. According to this conception, the name "glioma" is misleading and should be abolished. The authors reject Cushing and Bailey's classification and propose a simple classification into medulloblastoma and ganglioneuroma according to the nature of the specific tumor cells. The character of the stroma may be indicated by the adjectives "reticular," "syncytial" and "neuromatous."

W. SAPHIR.

NEOPLASTIC RUPTURE OF THE SPLEEN. M. PLONSKIER, Virchows Arch. f. path. Anat. **289**:370, 1933.

A man, aged 63, died of intraperitoneal hemorrhage due to spontaneous rupture of the spleen. Examination during life had brought to light marked anemia and leukocytosis (white cell count, 34,000), most of the cells being myelocytes. At necropsy a mass in the mediastinum was held to be a primary tumor. There were numerous metastases in all the organs, including the spleen, which weighed 540 Gm. and had ruptured. Histologically the tumor was suggestive of carcinoma in places, but its exact origin remained in doubt, although it was held to be probably a reticulo-endothelial sarcoma.

O. T. SCHULTZ.

LIPOIDS OF TUMORS OF THE SKIN. L. SZODORAY and P. SPANYÁR, Virchows Arch. f. path. Anat. **289**:493, 1933.

Thirty-one tumors of various kinds were examined by the various histochemical methods for fats and lipoid substances. In twenty-one of these tumors, which included seventeen tumors of the skin, quantitative chemical estimation of total fat, neutral fat, lipoids and cholesterol was also carried out. The neoplasms of the skin contained a relatively large amount of visible fat, which was not necessarily associated with an increase in total fat. The histochemical methods are not sufficiently specific to permit identification of the various kinds of fatty substances that may be present within the cells. The most striking finding in the tumors of the skin was an increase in cholesterol, which constituted from 5 to 21 per cent of the total fatty substances and more than 1 per cent of the dry weight of the tumor tissue.

O. T. SCHULTZ.

CALCIFYING EPITHELIOMA OF THE SKIN. W. FINK, Virchows Arch. f. path. Anat. **289**:527, 1933.

Calcifying epithelioma of the skin has been held by many to be a characteristic kind of epithelioma. In 1930 B. Fischer described calcification of atheromatous epidermal cysts, which raised the question whether all of the so-called calcifying

epitheliomas of the skin are true epitheliomas. Fink examined histologically nine such tumors and a number of atheromatous cysts. He concludes that the term calcifying epithelioma includes two kinds of structures. Some are true basal cell epitheliomas in which the epithelial parenchyma has undergone degeneration and fatty change. This is followed by connective tissue organization and calcification of the degenerated material, and sometimes by true bone formation. Others are atheromatous epidermal cysts in which inflammation of the capsule has led to penetration of organizing connective tissue into the fatty contents of the cyst and to calcification. If the epithelium has been completely degenerated it is impossible to decide the origin of the calcified tumor. Although the so-called calcifying epitheliomas may be either true epitheliomas or atheromatous cysts that have undergone calcification, the process is identical in both and is essentially one of organization of degenerated epithelium.

O. T. SCHULTZ.

BRANCHIOGENIC CARCINOMA IN A HORSE. P. KOSTER, Virchows Arch. f. path. Anat. **289**:544, 1933.

Although branchiogenic carcinoma of the neck is not uncommon in human beings, its occurrence in domestic animals has been described infrequently. The author describes a typical branchiogenic squamous cell carcinoma in a horse.

O. T. SCHULTZ.

COLLISION CARCINOMA AND SARCOMA. W. NOWICKI, Virchows Arch. f. path. Anat. **289**:564, 1933.

The author describes two neoplasms composed of an admixture of carcinomatous and sarcomatous tissue. One was a tumor of the mammary gland of a woman aged 45. In its peripheral portion it was pure glandular carcinoma. Centrally it was spindle cell sarcoma with numerous large, multinucleated giant cells. In an intermediate zone the two kinds of tissue were intermingled. The second tumor was a nodule that apparently arose from the wall of a bronchus. At the pole which had replaced bronchial tissues it was a bronchogenic carcinoma. At the opposite pole it consisted of spindle cell sarcoma. The midportion was composed of an admixture of the two kinds of tissue. The author interprets both tumors as the result of the independent development of carcinoma and sarcoma and of the invasion of one type of neoplastic tissue by the other where the two kinds came in contact. He discusses the nomenclature of tumors composed of both carcinomatous and sarcomatous tissue. For those that develop as two distinct types of neoplasm which become intermingled in the course of their growth he prefers the name collision carcinoma and sarcoma.

O. T. SCHULTZ.

ONCOCYTES IN SALIVARY GLANDS AND THEIR RELATION TO TUMORS. G. STEINHARDT, Virchows Arch. f. path. Anat. **289**:624, 1933.

Steinhardt's report is based on histologic examination of salivary glands in sixty-five necropsies, undertaken with the view of determining the correctness of Hamperl's assertion (*Virchows Arch. f. path. Anat.* **282**:724, 1933; abstr., ARCH. PATH. **15**:735, 1933) that tumors of the salivary glands and lympho-epitheliomas of the buccal cavity and pharynx may arise from cells that he termed oncocytes. These are derived from glandular and duct epithelium by a process which Hamperl termed senile differentiation. Steinhardt could find no oncocytes in any of his material, although he did find what Hamperl had described as a transitional form in eight cases, all occurring in persons over 60 years of age. Steinhardt agrees that these are senile cells. Nodular and papillary hyperplasias of such transitional cells were seen a few times. He does not agree that lympho-epitheliomas are derived from such cells or from oncocytes, but considers that they probably arise from branchial cleft rests. He describes a solid adenoma of the parotid gland.

O. T. SCHULTZ.

TUMORS OF THE FOURTH CEREBRAL VENTRICLE. B. KELLNER, Virchows Arch. f. path. Anat. **289**:656, 1933.

Two tumors of the fourth ventricle are described. One is considered an ependymal glioma; the other, an epithelioma derived from the covering cells of the choroid plexus.

O. T. SCHULTZ.

PRESENCE OF RECEPTORS M AND N IN TUMORS. ALFRED ZACHO, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:520, 1932.

The substances M and N were found in thirteen malignant tumors; they were absent in seven benign growths. The determination was based on absorption of purified immune serums containing the substances M and N by aqueous extracts of tumor tissues. Complement fixation was found unsuitable for the detection of substances M and N.

I. DAVIDSOHN.

SEROLOGIC ANALYSIS OF SARCOMATOUS TISSUE. E. WITEBSKY and E. MORELLI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:179, 1933.

The serum of rabbits treated with sarcomatous tissue reacted in complement-fixation tests most strongly with sarcoma extract, less with carcinoma extract, least with normal tissue extract and not at all with extract of rat or chicken sarcoma. The A group-specific quality could not be demonstrated in the sarcomatous tissue, although it was regularly present in the carcinomatous tissues of the same blood group. The reactivity of the immune serum was not due to a larger amount of lipoids in the sarcoma as compared with the normal organs. Adsorption of the immune serum with alcoholic extracts of normal organs removed the ability to react with those organs but left the ability to react with carcinomatous and sarcomatous extracts. Adsorption with carcinomatous extracts left only the reactivity with sarcomatous tissues. All antibody functions were removed by adsorption with sarcomatous extracts. The relation between sarcomatous and carcinomatous antigenic functions appears closer than that between the antigenic functions of sarcomatous and normal organs, with the exception of the spleen. The quality of the sarcoma immune serum depends more on the properties of the antigen than on the animal used for the injection.

I. DAVIDSOHN.

DEMONSTRATION OF ANTIBODIES AGAINST MALIGNANT TUMORS IN BLOOD. HANS J. FUCHS, M. V. FALKENHAUSEN and W. K. DEVRIENT, Ztschr. f. Immunitätsforsch. u. exper. Therap. **78**:272, 1933.

Fuchs has worked out a test for malignancy which is based on determination of the nonprotein nitrogen in a mixture of the fibrin or of a specially prepared precipitate of the serum of patients with malignant tumors with the serum of normal persons, and vice versa. The fibrin and serum of affected persons may contain an antigenic substance specific for malignant growths, or antibodies directed against the tumor antigen. The presence or absence of such antibodies is determined by the phase of the disease and by the immunity responses of the body. Thus, a mixture of the serums of two carcinomatous patients may show a decrease of the nonprotein nitrogen, indicating a positive reaction, if the patients are at the time in different phases of the disease, or no such change if both are in the same phase. The method can also be used for the study of other diseases in which antibodies are produced.

I. DAVIDSOHN.

MALIGNANT GIANT CELL TUMOR OF BONE. W. I. KORCHOW, Ztschr. f. Krebsforsch. **38**:380, 1933.

The author gives a detailed description of a case of so-called giant cell sarcoma of the tibia, with ultimate death. There were numerous metastases, both local and generalized. In these metastases there was complete absence of the giant

cells, except in some of the tumors in the skin close to the original growth. The structure was that of malignant development of the tumor stroma. Korchow, in common with most recent writers on these tumors, regards the primary giant cell growth as dystrophic rather than neoplastic, with, in such cases as that discussed here, a secondary and superposed malignant alteration. H. E. EGGERS.

CARCINOMA OF THE ALIMENTARY TRACT AT EARLY AGES. G. WOLFF, Ztschr. f. Krebsforsch. **38**:409, 1933.

Wolff bases his rather elaborate study of the incidence and course of carcinoma of the alimentary tract at relatively early ages both on cases seen at the clinic of Freiburg University and on those reported in the literature. He finds that precocious cancers occur with special frequency in this location (in about 69 per cent of cases). The upper part of the tract, from the mouth to the stomach, is rarely involved primarily. The growths occur in the stomach with frequency, about 25 per cent of such carcinomas being primary here; they originate in the intestine, exclusive of the rectum, in from 10 to 15 per cent of the cases, and in the rectum the frequency of primary involvement is about the same as in the stomach, or 25 per cent. As to the accessory organs, primary cancer of the liver, always rare, occurs with rather surprising frequency in young persons, about 4.5 per cent of all carcinomas in children originating here. Precocious cancer is rare in the gallbladder and pancreas. There are no apparent differences in sex incidence, nor do such cancers show any definite peculiarities of course, except that in Wolff's experience the course appears to be somewhat accelerated. The etiology is discussed principally in terms of Virchow's irritation theory versus that of displacement as advocated by Cohnheim and Ribbert. H. E. EGGERS.

RELIABILITY OF STATISTICS ON CANCER. A. E. SITSEN, Ztschr. f. Krebsforsch. **38**:639, 1933.

In this critical discussion of the value of statistics on cancer, Sitsen divides them into three classes as regards source: (1) those drawn from autopsy reports of various pathologic institutions, (2) those from mortality reports, and (3) those from reports based on clinical findings. As regards the first, their evidence is as a rule accurate, but their availability for general conclusions is affected by the limited character of the clientele of the institutions and by the fact that, particularly in the charitable institutions, the types of cases vary with the interests of the responsible members of the staffs and with the general effectiveness of treatment, since with fewer deaths from other diseases those from cancer will show a corresponding increase. Statistics on mortality are of general application but are open to the patent objection of questionable diagnosis—a factor which cannot be evaluated even approximately. With statistics from clinical sources there is even greater liability to error through inaccurate diagnosis, but they have the great advantage of giving information as to current cases rather than as to those that have terminated in death. In Austria a systematic effort is being made to collect information of this sort comprehensively and without reduplication. No statistics on cancer from a single source are satisfactorily accurate, but the errors lie not in the methods of collection but in their execution. Ideal use of all three sources is attainable, as is indicated in the collection of statistics in the Dutch East Indies by Snijder and Straub; they have, for their district, reports of complete physical examinations of the entire population, and over 90 per cent of patients who die come to autopsy. Such results can be achieved generally only by education of the populace to the fundamental importance of routine autopsies. H. E. EGGERS.

WHAT SHOULD BE MEANT BY THE TERM "PRECANCER"? H. T. DEELMANN, Ztschr. f. Krebsforsch. **38**:648, 1933.

The term "precancer," widely used by clinicians, is according to Deelmann objectionable since it is used to include conditions in which cancer is only a probability or even only a possibility. To the pathologist the word should convey

a definite significance—that of the local "unrest" of cellular elements which so frequently precedes the infiltrative growth that constitutes developed cancer. Changes of this sort are not infrequently seen most typically at the margins of carcinomas and appear there to indicate a radial transmission of cancerous activity to cells originally not involved. Disordered and evidently excessive epithelial growth of this type, as yet without actual infiltration, certainly is not cancer, but as indicating a change immediately precedent to infiltrative growth it is precancerous in the strictest sense.

H. E. EGGERS.

Medicolegal Pathology

TESTS FOR M AND N BLOOD GROUPS. W. CROME, Deutsche Ztschr. f. d. ges. gerichtl. Med. **21**:435, 1933.

The tests should be made by persons skilled in serologic technic. The results of 3,800 serologic observations are recorded. The simultaneous absence of M and N factors was never observed. Of the entire series, 19.6 per cent belonged to group N, 30.8 per cent to group M and 49.6 per cent to group M N. According to the four group scheme, there were 39.7 per cent in group O, 47.7 per cent in group A, 9.6 per cent in group B and 3.5 per cent in group A B. A study of heredity in 32 families with 82 children showed that the mendelian laws were strictly followed. Four pairs of monozygotic twins had the same blood group. In a series of 46 paternity tests, 3 persons were excluded as possible fathers on the basis of the M and N groupings.

JACOB KLEIN.

PENTAMETHYLENETETRAZOL POISONING. A. ESSER and A. KÜHN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **21**:474, 1933.

A 22 year old man died one hour after drinking 100 cc. of a 10 per cent solution of pentamethylenetetrazol with suicidal intent. Clinically there was observed a state of excitation and convulsions simulating jacksonian epilepsy. Macroscopically the viscera appeared normal. Microscopically there were marked hyperemia of all the organs, cloudy swelling of the liver and kidneys, a great decrease in the suprarenal lipoids, fatty changes in the liver and fragmentation and fatty changes in the myocardium. Animals experimentally poisoned showed similar changes. Pentamethylenetetrazol could be demonstrated in all parts of the body and in its fluids. One third of the ingested amount was recovered from the tissues. Experiments demonstrated that this substance could be recognized even in putrefying organs. The drug is absorbed chiefly from the stomach and excreted mainly through the kidneys. The pharmacologic views as to the fleeting action of pentamethylenetetrazol do not hold for the toxic dose. Animals receiving slightly toxic doses have shown effects after twenty-four hours. Some have apparently recovered only to die after several days. It is estimated that the minimum lethal dose is 7.8 Gm. of pure pentamethylenetetrazol for an adult human being weighing 65 Kg.

JACOB KLEIN.

CHARACTERISTIC SKIN MARKINGS AFTER FALLING INTO THE WATER FROM A HEIGHT. GYULA BALAZS, Deutsche Ztschr. f. d. ges. gerichtl. Med. **21**:515, 1933.

Persons who have jumped into the water from a bridge (10 meters high) and have been saved have shown characteristic anemic areas on the skin in the area which hit the surface of the water. These anemic regions, and even hematomas, occur most commonly over the thigh and gluteal region, particularly over the femur and the obturator foramen, and result from pressure of the tissues against the bony framework. After twenty-four hours the cutaneous changes begin to diminish, and they disappear after from three to four days unless there is a hematoma. The markings have been seen in 15 of 250 cases. They indicate a vital reaction on falling into water from a height and may give an indication as to the position of the body when it hit the water.

JACOB KLEIN.

Society Transactions

PATHOLOGICAL SOCIETY OF EASTERN NEW YORK

ARTHUR W. WRIGHT, *Secretary*

Regular Meeting, April 7, 1933

F. F. HARRISON, *Presiding*

FATAL ERYTHROBLASTIC ANEMIA. V. C. JACOBSEN.

An Italian boy, 3 years of age, had had enlargement of the spleen and liver for two years. The spleen filled the entire left side of the abdomen and extended down into the pelvis. There was weakness. The hemoglobin was 40 per cent; the erythrocyte count, 2,800,000; the leukocyte count, 22,600, with 73 per cent polymorphonuclears, 20 per cent lymphocytes and 7 per cent myelocytes. Fifty nucleated red blood cells were seen. There was slight persistent fever. The treatment consisted of blood transfusion, application of 800 milligram-hours of radium and later administration of liver extract no. 55.

After eight months the spleen was still greatly enlarged. The hemoglobin was 28 per cent. The erythrocyte count was 2,400,000; the leukocyte count, 16,600, with 25 per cent polymorphonuclears, 2 per cent basophils, 40 per cent lymphocytes, 17 per cent monocytes and 16 per cent myelocytes. Sixteen nucleated red blood cells and 30 reticulocytes were seen. Liver extract was given intravenously, without improvement. Death occurred from a respiratory infection.

At necropsy, the abdomen was distended and prominent while the remainder of the body showed marked emaciation. The mesenteric lymph nodes were large and pale. The spleen weighed 450 Gm. and occupied the entire left side of the abdomen. The surface showed hyaline capsulitis. The organ was firm, rather rectangular and brickish red. Sections showed a firm, grayish-red, bulging, finely granular pulp. The lymphoid tissue was indistinct. The liver weighed 940 Gm. and was pale chocolate-brown. Section revealed a pale parenchyma containing numerous small foci of necrosis. The kidneys were of normal size and extremely pale except for a few petechial hemorrhages. The muscles were pale grayish red and thin. The bone marrow of the ribs was small in amount and pale. The vertebral marrow was dry and congested, with a few pale areas scattered throughout. The marrow of the ilium was congested and apparently more cellular than usual.

Microscopic examination of the spleen showed obliteration of many sinuses and atrophy of the follicles. Many foci of mononuclear cells of myeloblast and erythroblast types were present with eosinophilic myelocytes and mature polymorphonuclears in small numbers. Megakaryocytes were numerous, as well as large cells resembling the Dorothy Reed cells of Hodgkin's disease. Very little hemosiderin was found. In the liver, foci of acute hyaline necrosis with invasion by polymorphonuclears were present. Much hemosiderin was found in both hepatic and Kupffer cells. The kidneys were edematous, and there was an increased amount of lipoids in the cortical tubules. The bone marrow from whatever location was very cellular, with marked hyperplasia of the erythrogenic centers. Many myeloblasts and erythroblasts of large and small types were present, as were polymorphonuclears of all stages and many eosinophils and megakaryocytes. There was no phagocytosis of erythrocytes, and hemosiderin was not observed. Bone trabeculae were abundant and normal.

The clinical and postmortem observations were typical of a type of blood dyscrasia seen in childhood and known as erythroblastic anemia. Many of the cases reported have occurred in the Mediterranean races, as did this case.

SARCOMA OF THE CHOROID. STEPHEN H. CURTIS.

A woman, 62 years of age, first noticed in October, 1931, that the sight of her right eye was failing. Gradually she began to suffer severe pain in this eye, the pain being more severe at night. The conjunctiva of the eye was injected and the orbit protruded slightly.

Physical examination of the eye showed moderate exophthalmos, mild acute conjunctivitis, increased intra-ocular tension and paralysis of the pupil. The ophthalmoscope revealed a dark red mass protruding from the retina medial to the optic nerve. The retina about the tumor was detached.

The eye was enucleated in January, 1932. Externally it showed nothing of note. On section a firm, pedunculated, cauliflower-like mass, 1 cm. in diameter, was found projecting from the retina near but not involving the optic nerve. Cut surfaces of the mass were pearly gray, smooth and glistening.

Microscopically, the tumor was composed of two types of cells, which were probably variants of a parent cell. One type was long, spindle-shaped and afibrillar, with oval, pale-staining nuclei. The other was large, round or polyhedral, with abundant cytoplasm and large, pale, often cystic nuclei. Moderate numbers of the cells of both types contained melanin. No neurofibrils or rosettes could be found. Mitoses were absent. Stroma was not abundant.

This tumor presented the characteristics of a nonpigmented or at most very slightly pigmented melanosarcoma of the choroid. By some pathologists, however, the tumor was thought to be a neurogenic sarcoma of the retina. The evidence, both clinical and pathologic, favors the former diagnosis.

UNUSUAL LIPOID CHANGE IN AN OVARIAN FIBROMA. ELLIS KELLERT.

A woman, 43 years old, unmarried, had had pelvic pain, backache and abdominal enlargement for nine months. Both the tubes and the ovaries were removed. One tube was attached to a parovarian cyst 7.5 by 5 by 3 cm. in size. The opposite ovary was replaced by a tumor 13 cm. in diameter. The serosa was smooth, gray and traversed by many prominent blood vessels. On section there was found a yellowish, solid tumor containing a single large and several small cavities, which were empty and collapsed. To their linings were attached shaggy fibrinous masses of clot and a small amount of grayish-yellow amorphous material. The thick, solid portion of the growth was at the attached margin of the ovary. Its cut surface was rough, fibrous and bright yellow.

Microscopic sections showed interlacing bands of spindle-shaped cells containing short, oval, deeply staining nuclei and resembling ovarian stroma. There were no mitoses. The intercellular substance was variable in amount and, where abundant, was associated with an enormous number of fat globules, which varied greatly in size and were found both within and between the cells. There were no distinct adipose cells. In sections where the fat had been dissolved with chloroform, only a cribriform connective tissue network containing many of the oval nuclei was seen.

On prolonged immersion of the tissue in solution of formaldehyde the yellow color faded and became gray. The changes observed were probably degenerative and were perhaps due to circulatory disturbances.

MENINGIOMA OF THE LEFT CEREBRAL HEMISPHERE. ELLIS KELLERT.

A woman, aged 40, had had severe intermittent headaches and occasional convulsions for four years. Recently jacksonian epilepsy developed with twitching of the right side of the body and of the face. The right hand was weak, and sight was poor in the right eye. When speaking, the patient would frequently hesitate because she could not find the right word. A clinical diagnosis of tumor of the right hemisphere was made.

The brain weighed 1,440 Gm. In the left frontoparietal region there was a globular tumor, 7 cm. in diameter, attached to the dura and pushing into the brain. During the handling of the brain the tumor enucleated spontaneously. It was

encapsulated and on section appeared grayish white and solid with granular cut surfaces. Sections showed a very cellular growth consisting of spindle-shaped cells of fairly uniform size, having a whorl-like arrangement. Mitotic figures were not found. A diagnosis of meningioma was made.

A Mixed Tumor of the Urinary Bladder. G. H. Klinck, Jr.

A white girl, 16 years of age, had been having increasing difficulty in voiding for several months. She discovered that if she inserted her finger into the urethra she could void. Cystoscopic examination showed a soft, pedunculated tumor, the size of an orange, attached just within the orifice of the right ureter. The tumor was removed by suprapubic cystotomy. It was a soft, globular mass about 7 cm. in diameter. The surface was slightly uneven, some areas being smooth and pale, others slightly roughened and congested. There was a very delicate and easily broken capsule. The pedicle measured 6 mm. in length and 3 mm. in diameter. Section revealed soft, myxomatous, semitranslucent tissue with slightly opaque foci. Microscopically, the tissue was largely myxoma but with coarse strands of fibrous tissue. Sections from the surface showed acute inflammation. A diagnosis of fibromyxoma was made.

The patient was entirely well for a year; then hematuria developed. A tumor was found within the bladder at the site of the suprapubic incision. It was irregularly distributed along the line of the old incision. This area, including the tumor, was removed, the mass being approximately 30 cc. in volume. Grossly, the tissue resembled the original tumor. Nine hundred and fifty milligram-hours of radium were applied to the edges of the new suprapubic incision before closing the wound.

Microscopic study showed a myxomatous growth like that found previously but containing, in addition, small islands of cartilage and numerous striated and smooth muscle fibers. It is probable that both cartilage and muscle were present in the original tumor but were not found in the sections made.

Two months after the second operation, a recurrence appeared in the healed wound of the cystotomy. The right ureter was normal. When the patient was last seen, six months after the final operation, there was an increase in the size of the midline growth. A biopsy showed all of the features previously described.

The tumor was a teratoma, although only mesodermic elements were present, namely, striated and smooth muscle, myxomatous connective tissue and cartilage. It was not histologically malignant, but recurrences developed probably on the basis of cells left behind at the various operations and also seeded along the operative incisions.

Book Reviews

Wilhelm Conrad Röntgen and the Early History of the Roentgen Ray. By Otto Glasser, Ph.D., Director, Radiation Research Department, Cleveland Clinic. With a chapter on personal reminiscences of W. C. Röntgen, by Margaret Boveri (Berlin). Price, $6. Pp. 496, with 96 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1934.

This book is a translation with corrections and revisions of the original German edition of 1931, which was well received. It is the product of the cooperation of three publishers, Julius Springer of Berlin, Charles C. Thomas of Springfield, Ill., and John Bale, Sons and Danielsson, Ltd., of London. The book is printed by the last named firm. The paper is heavy and highly glazed, which is unfortunate. The first four chapters describe vividly the details of the discovery in 1895 of the roentgen rays, the circumstances of its announcement and the first reception. The biographic interest of the book centers in the fifth chapter (147 pages). The first part of this chapter portrays well the life and intellect of Wilhelm Conrad Röntgen. The second part contains personal reminiscences of Röntgen by Margaret Boveri, the daughter of Boveri the zoologist, who was Röntgen's colleague in Würzburg and probably his most intimate friend. These interesting reminiscences touch on Röntgen's youth and student life, his friends, the war, science, art and his last years. In this chapter are scattered many letters, some in facsimile, which give intimate contact, as it were, with a great personality. The reading of this most interesting chapter leaves the impression that it is a worthy account, sympathetic but truthful, of the life and character of Röntgen. Two quotations may be permitted by way of illustration:

"The salient feature of Röntgen's work . . . was his persistence and his critical honesty in making observations and measurements. He approached the solution of physical problems with great acuity and relentless thoroughness. Over and over again he worked out new control experiments in order to convince himself thoroughly of the absolute accuracy of the results which he had obtained, and with great scepticism he always warned against accepting any hypothesis which was not based upon sound experimental evidence. Therefore the results of his work which were published in his papers are distinguished by a rare reliability combined with remarkable classical brevity and simplicity." [Glasser, p. 74.]

"Perhaps Röntgen's most outstanding characteristic was his absolute integrity. Integrity in science, integrity in judging people even though appearances were deceiving, and integrity in faithful devotion to his friends though their opinions might be at variance. True, there were sometimes hardness and gruffness towards strangers and sometimes sudden anger toward those close to him, but these moments were overbalanced by the continuous warmth of his kindliness and readiness to help, which ever again broke through the shy exterior and produced a deep and rare sense of security and confidence." [Margaret Boveri, p. 196.]

The remaining chapters are concerned with the various aspects of the early history of the roentgen rays and their applications. Chapter 23, the bibliography, gives a list of articles about Röntgen and lists of books, pamphlets and papers—1,044 separate items—on the roentgen rays, published in 1896. Glasser's book is a noteworthy addition to the history of science. The ninety-six illustrations add greatly to the value and interest of the presentation. In its special field it will be a great landmark and a source of information for all students of the roentgen rays and their discoverer.

Die Spezifizität der serologischen Reaktionen. By K. Landsteiner. Price, 8.80 marks. Pp. 123, with 22 tables and 1 illustration. Berlin: Julius Springer, 1933.

Since 1875, when Landois first studied normal hemagglutinins, attempts to answer the question of the nature of antigens and antibodies have been so numerous that it is becoming more and more difficult for the student of immunology to separate the good from the valueless. To those who are trying with varying success to

keep up with the ever increasing avalanche of publications in this field, Landsteiner's monograph will be a welcome summary. Some long and particularly important chapters of books on modern immunology are the work of Landsteiner. No wonder that the book impresses one like a condensate of Landsteiner's life-work! His work serves as a background against which the important contributions of others are projected after they have been subjected to his critical evaluation.

The amount of information crowded into 95 pages of text shows marked ability to make every word count. This brevity and precision are laudable, and may be construed as an expression of his confidence in his readers. The value of the book is further enhanced by lucidity in the presentation of the material, none of which has been sacrificed for the sake of compactness. The reviewer does not recall having read an equally clear presentation of certain particularly complicated aspects of the chemistry of antigens.

The book is divided into six chapters. An analysis of the concept of serologic specificity is given in the introduction. The second chapter deals with the serologic specificity of proteins and with the effect of artificially produced chemical changes in the antigen. In the following chapter the specificity of cell antigens is presented, and the methods of differentiating between closely related species by means of cross-absorption are described. The iso-antibodies, the dissociation of bacteria, the heterophilic reactions, the lipoidal and carbohydrate haptens, the hypothetic structure of antigenic fractions of the cells and the serologic differentiations of individuals and species are also discussed. Then comes a chapter on the specificity of normal and immune antibodies. The degree of concentration in this chapter of 7 pages, with a bibliography of 97 references, may be illustrated by the fact that Ehrlich's hypothesis of the side chain is disposed of in a paragraph of 11 lines, and by the fact that only 30 lines are needed to give a clear presentation of the hypothesis of the origin of antibodies directly from the antigens. Chapter 5 is an admirable presentation of the serologic reactions with artificial complex antigens and simple chemical substances. While the book is not intended for the beginner, this particular chapter impresses the reviewer as a clear introduction to one of the most difficult branches of immunology. The last chapter summarizes the recent contributions to the present knowledge of specific substances of the cell, and is particularly concerned with the antigenic properties of carbohydrates and lipoids. The bibliography includes 966 references, each of which is considered in the text, and, in addition, a list of standard texts and monographs. The titles of 42 articles which appeared while the book was being printed are appended. The results of the author's recent and previously unpublished investigations are included, as, for example, a study of the distribution of the Forssman antigen (page 45) and an application of the azoprotein method to aliphatic compounds (page 83) and to peptides (page 85).

Le poison des amanites mortelles. By R. Dujarric de la Rivière. Price, 60 francs. Pp. 182, with 24 plates. Paris: Masson et Cie, 1933.

In the introduction the author discusses the history of poisonous fungi. Then follow chapters on the botanical description of Amanita phalloides and related forms; on the chemistry of the toxic principle; on the physiologic action of the poison; on the clinical phenomena and the structural changes following Amanita poisoning; on the medicolegal problems of poisonous fungi, including the detection of various fungi of this kind by study of the spores; on treatment and on prophylaxis, with particular reference to the conditions in France. There are twenty-four plates, four of which are in colors. At the end is a bibliography of some 500 references. The American literature receives adequate consideration. The monograph gives a thorough review of the present knowledge of poisoning by the "deadly Amanita."

Books Received

ANNUAL REPORT OF THE SURGEON GENERAL OF THE PUBLIC HEALTH SERVICE OF THE UNITED STATES FOR THE FISCAL YEAR 1933. Price, 75 cents. Pp. 128. Washington: United States Government Printing Office, 1933.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY. VOLUME IX. INFLUENZA (PART 1), WITH SPECIAL REFERENCE TO THE PART PLAYED BY PFEIFFER'S BACILLUS, STREPTOCOCCI, PNEUMOCOCCI, ETC., AND THE VIRUS THEORY. D. and R. Thomson. Price, $8. Pp. 640, illustrated. Baltimore: Williams & Wilkins Company, 1933.

This is the first part of a huge monograph in two parts on influenza. The object is to summarize in convenient form the information in some four thousand publications on this disease. The present volume deals with the history, the clinical features and the epidemiology of influenza, but the greater part of it is devoted to the results of the investigations of the etiology. The literature on the relationship to influenza of Pfeiffer's bacillus, streptococci, pneumococci and other bacteria as well as of filter-passing "virus" is reviewed. The authors give an account of their own bacteriologic work on influenza which is illustrated with twenty-eight plates of photographs. The second part will deal "with the bacteriology of the complications of influenza as well as with the pathology, the treatment, and prevention of the disease," after which will follow "the vast bibliography of over 4000 references, as well as a very complete authors and subject index." Obviously the full scope and merits of the monograph will not become apparent until the second part is published.

LABORATORY MEDICINE: A GUIDE FOR STUDENTS AND PRACTITIONERS. Daniel Nicholson, M.D., Member of the Royal College of Physicians, London; Assistant Professor of Pathology, University of Manitoba; Assistant in Pathology, Winnipeg General Hospital, Winnipeg, Canada. Edition 2, thoroughly revised and much enlarged. Price, $6.50. Pp. 566, with 124 engravings and 3 colored plates. Philadelphia: Lea & Febiger, 1934.

The first edition appeared in 1930 and was reviewed in the ARCHIVES (**11**:168, 1931). The second edition is an improvement on the first, and it presents well the indications, methods and interpretations of the diagnostic laboratory tests most suitable for current use in medical practice.